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St. Francis Hotel, San Francisco, California, June 22-25, 1950

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OF THE

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VOL. XVII MAY 1950 No. 5

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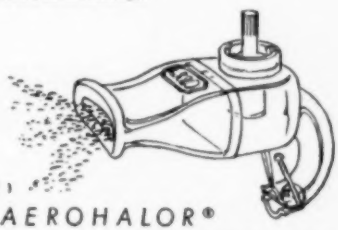

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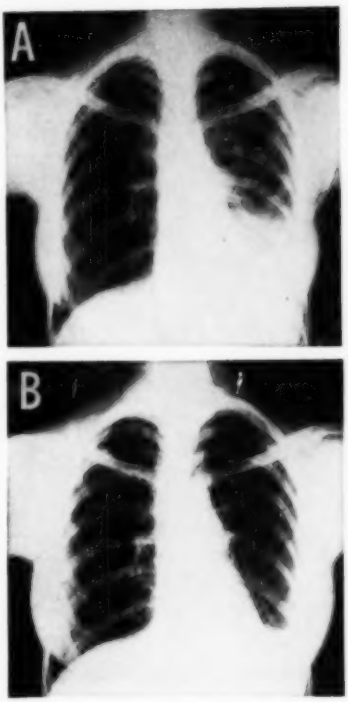

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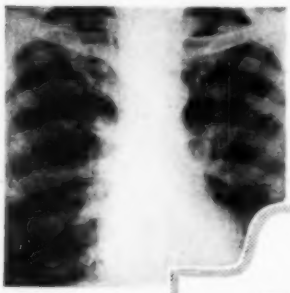

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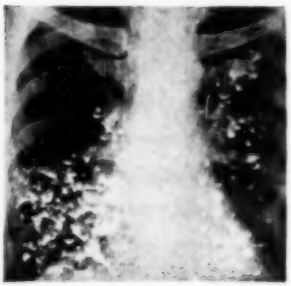

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Smadel, J. E.: J.A.M.A. *142*:315, 1950 (discussion)

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Hewitt, W. L., and Williams, B., Jr.: New England J. Med. *242*:119, 1950

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Payne, E. H.; Knaudt, J. A., and Palacios, S.: J. Trop. Med. & Hyg. *51*:68, 1948

"NO symptoms or signs of toxic effects attributable to the drug were observed."

Ley, H. L., Jr.; Smadel, J. E., and Crocker, T.: Proc. Soc. Exper. Biol. & Med. *68*:9, 1948

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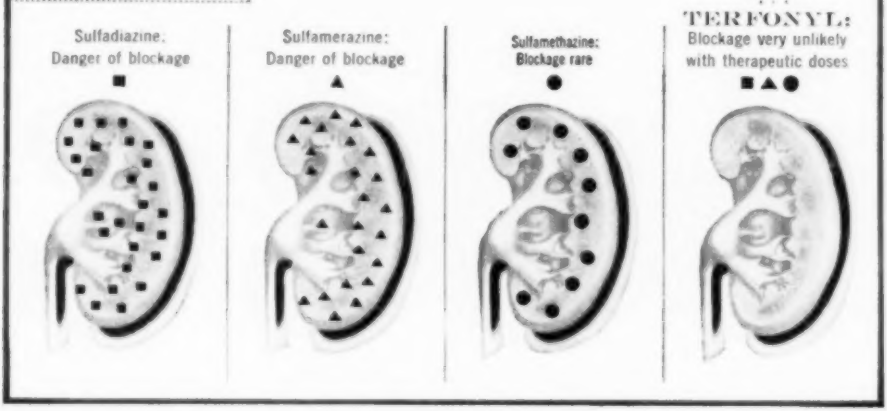

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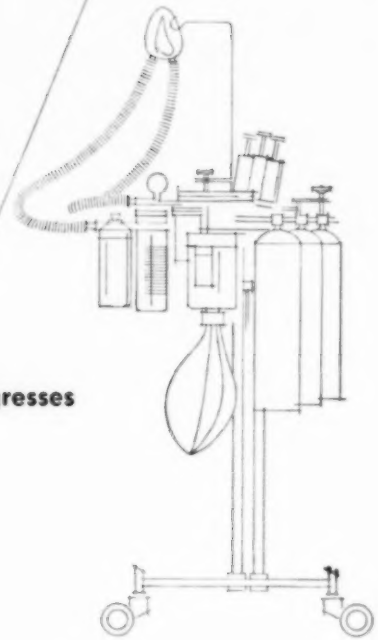

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DISEASES *of the* CHEST

VOL. XVII MAY 1950 NUMBER 5

Neomycin in Experimental Tuberculosis of Guinea Pigs

ALFRED G. KARLSON, D.V.M., Ph.D.,**
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WILLIAM H. FELDMAN, D.V.M., D.Sc.**
Rochester, Minnesota

The administration of neomycin has been found to increase the survival time of mice infected either intravenously[1] or intracerebrally[2] with virulent human-type tubercle bacilli. In this report we present data showing that the administration of neomycin to tuberculous guinea pigs had a marked beneficial effect on the disease even when treatment was delayed until the infection was well established.

Methods

Thirty male guinea pigs weighing approximately 800 gm. each were each inoculated subcutaneously over the sternum with 0.1 mg. (moist weight) of virulent human-type tubercle bacilli (H37Rv). Twenty-one days later 4 animals (pretreatment controls) were killed and found to have grossly visible lesions of tuberculosis as shown schematically in figure 1. Subsequent histologic examination revealed actively progressing lesions of tuberculosis at the site of inoculation, axillary lymph nodes, spleen, liver and lungs. On the twenty-first day of infection each of the remaining 26 animals was found to have an abscess at the site of inoculation and enlarged axillary lymph nodes. It is presumed that these animals had tuberculous involvement of the lungs, liver and spleen comparable to that seen in the pretreatment controls.

The 26 animals were divided in three groups consisting respectively of 10 untreated animals, 6 animals each treated with 6 mg.

*Research Assistant, Mayo Foundation, Rochester, Minnesota.
**Division of Experimental Medicine, Mayo Foundation, Rochester, Minn.

of streptomycin daily and 10 animals treated with neomycin.* Treatment started on the twenty-first day of infection and continued for 77 days. The daily dose of 6 mg. of streptomycin was selected for comparison with the results obtained with neomycin since this amount of streptomycin has been shown to effect a marked regression and healing of experimental tuberculosis in guinea pigs.[3] No data were available regarding the toxicity of neomycin for guinea pigs. A dosage schedule of 2,000 neomycin units given twice daily in the axillary space was arbitrarily selected for trial. This was increased on several occasions when it was found that the drug was well tolerated judging by the maintenance of body weight. The final dose schedule was as follows: 2,000 units twice daily for 6 days; 4,000 units twice daily for 20 days; 6,000

*The neomycin, which contained 160 neomycin units per mg. was furnished through the courtesy of Dr. H. F. Hailman, The Upjohn Company, Kalamazoo, Michigan.

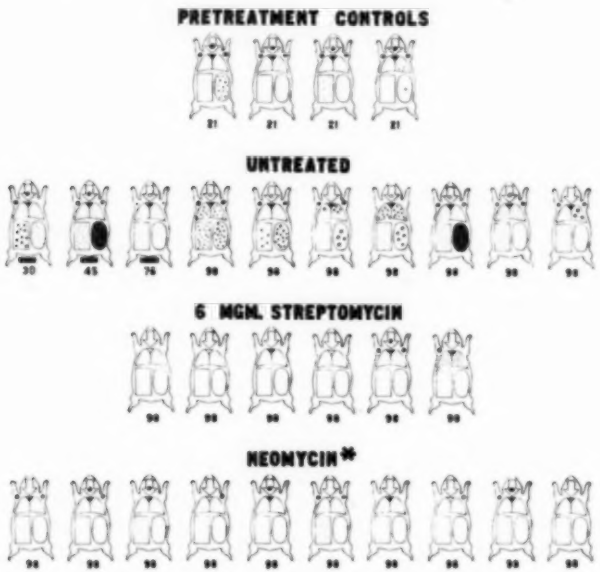

FIGURE 1: Schematic presentation of the extent of tuberculosis seen at necropsy. The rectangle and oval represent the liver and spleen respectively. Miliary and nodular lesions are indicated by small and large dots. The large dot or circle in the arrow indicates an abscess or an ulcer at the site of inoculation. The numerals show the number of days of infection and the black bar indicates that the animals died before the end of the experiment. *Dosage of neomycin: 2,000 units twice daily for 6 days, 4,000 units twice daily for 20 days, 6,000 units twice daily for 24 days, 8,000 units twice daily for 27 days.

units twice daily for 24 days, and finally 8,000 units twice daily for 27 days for a total of 77 days of treatment.

All the surviving animals, including the untreated animals, were killed at the end of the 77 days of treatment. Blood specimens were obtained for the determination of the concentration of neomycin. A record was made of the extent of tuberculosis seen at necropsy and tissues were preserved for subsequent histologic examination.

Results

Deaths: None of the animals treated with neomycin or with streptomycin died during the experiment. Three of the untreated animals died on the 30th, 45th, and 76th day of infection respectively and each had extensive tuberculous disease as shown in figure 1.

Drug Tolerance: The administration of neomycin appeared to be well tolerated judging by the appearance of the animals and the maintenance of body weight. After the dose of neomycin was increased from 4,000 units twice daily to 6,000 units twice daily there was a slight average weight loss of 15 gm. which persisted for 14 days. The weight loss was regained and the animals showed a slight gain in weight even after the dose was increased to 8,000 units of neomycin twice daily. During the entire treatment period the animals given neomycin gained an average of 25 gm. as compared to an average gain of 45 gm. for the untreated animals.

Concentration of Neomycin in Serum: Pairs of animals were bled by cardiac puncture at 0.5, 1.0, 1.5, 2.0 and 2.5 hours respectively following the last injection of 8,000 units of neomycin. The concentration of neomycin in the serum was determined by the cup-plate method using Staphylococcus aureus as the test microorganism.* The results are recorded in table 1. It is unfortunate that data are not available for periods longer than 2.5 hours. It appears that the level of neomycin in the serum of guinea pigs may decline rapidly.† The concentrations recorded in table 1 far exceed the amount of neomycin required to inhibit the growth of human tubercle bacilli in liquid medium. Using neomycin from the same source and lot number as used in this animal experiment, preliminary observations by Dr. G. M. Needham[4] indicate that human-type tubercle bacilli are inhibited by at least 0.5 neomycin unit per ml. of Proskauer and Beck liquid medium containing 10 per cent serum.

*The determinations of neomycin in the serum were done by Dr. F. R. Heilman, Section on Bacteriology, Mayo Clinic.

†In an experiment now in progress it has been found that in guinea pigs only a trace of neomycin is detectable twelve hours after injecting 8,000 neomycin units.

TABLE 1

Concentration of Neomycin in Guinea Pig Serums

	UNTREATED			HOURS AFTER LAST INJECTION OF 8,000 UNITS OF NEOMYCIN									
				0.5		1.0		1.5		2.0		2.5	
Animal No.	1	2	3	4	5	6	7	8	9	10	11	12	13
Concentration of neomycin in serum*	Tr.	0	Tr.	27.6	23.0	30.4	28.8	13.0	13.8	9.7	18.4	11.9	5.8

Tr. = Trace of activity. * = In neomycin units per ml. of serum.

TABLE 2

Average Severity of Tuberculosis Expressed Numerically Based on Histopathologic Characteristics[5]

Group No.	Treatment	Animals	Spleen (Max. 35)	Lungs (Max. 30)	Liver (Max. 25)	Site of Inoculation (Max. 10)	Average Index of Infection (Max. 100)
1	None*	4	15.0	2.5	7.5	10.0	35.0
2	None	10	21.0	17.5	16.0	10.0	64.5
3	Neomycin	10	1.3	0.0	5.8	8.1	15.2
4	6 mg. streptomycin daily	6	3.3	1.6	3.0	3.5	11.4†

* Pretreatment control animals killed 21 days after infection.

† This includes the tissues of a single animal with an index of infection of 50 in spite of the record that it was treated with streptomycin. If we exclude this animal the average index of infection will be 2.7 which is within the usual range for tuberculous guinea pigs treated for this length of time with 6 mg. of streptomycin daily.

Necropsy Findings: The observations made at necropsy presented impressive evidence that the administration of neomycin had a definite deterrent effect on the disease. The extent of tuberculosis seen in each animal is schematically recorded in figure 1. Among the 10 untreated animals the disease was severe in 7, moderate in 2 and minimal in 1. With one exception all the untreated guinea pigs had visible evidence of pulmonary tuberculous involvement. In striking contrast was the situation in the animals treated with neomycin. Referring to figure 1, it is seen that only 1 animal had grossly evident pulmonary involvement and this consisted of a few small grayish areas at the base of the left lung which subsequently proved to be healed fibrotic scars. Although the tracheobronchial lymph nodes appeared to be enlarged in 7 of the 10 animals given neomycin it was later found on microscopic examination that only 3 of the 7 had residual areas of active tuberculosis in this location. This was in sharp contrast to the untreated controls in each of which the enlarged tracheobronchial lymph nodes had grossly visible caseous foci.

Six of the 10 animals given neomycin had no apparent tuberculous involvement of the lungs, liver or spleen whereas every un-

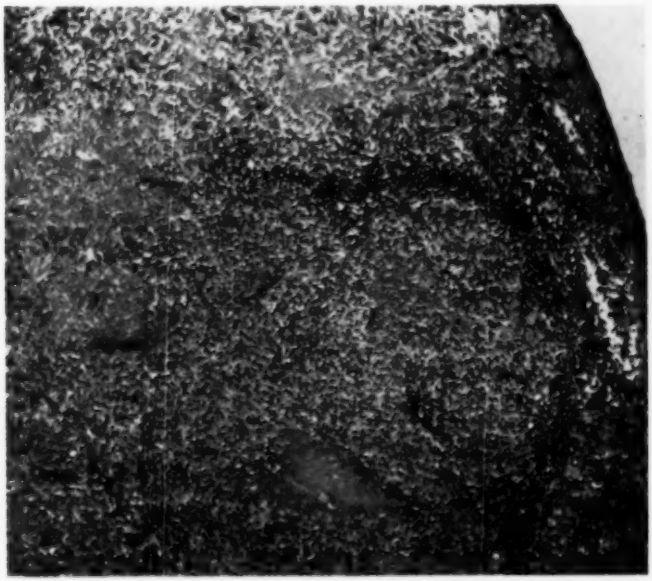

FIGURE 2: Spleen of an untreated guinea pig killed 98 days after infection with 0.1 mg. of virulent tubercle bacilli. There is replacement of the normal splenic pulp by large conglomerate tubercles (x64).

treated animal had lesions in at least one of these organs as shown in figure 1. It should be pointed out that there persisted in all but 2 of the animals treated with neomycin abscesses at the site of inoculation or caseous foci in the axillary lymph nodes in spite of the marked inhibition and regression of the disease in the parenchymal organs.

Of the 6 animals treated with 6 mg. of streptomycin daily, 4 had no disease that could be seen at necropsy. One animal had miliary lesions in the lungs, liver and spleen for which we are unable to account. Subsequent histologic examination revealed that this guinea pig did have actively progressing tuberculosis in spite of the record that it had been treated with 6 mg. of streptomycin daily for a period of 77 days. According to our experience this is very unusual. In 1 animal the lungs had grayish solid regions which microscopically were found to be nontuberculous.

If we exclude from the comparison the single animal that for unknown reasons did have active tuberculosis in spite of treatment with 6 mg. of streptomycin, it is apparent that the results achieved by 6 mg. of streptomycin may be superior to the results achieved by the administration of neomycin.

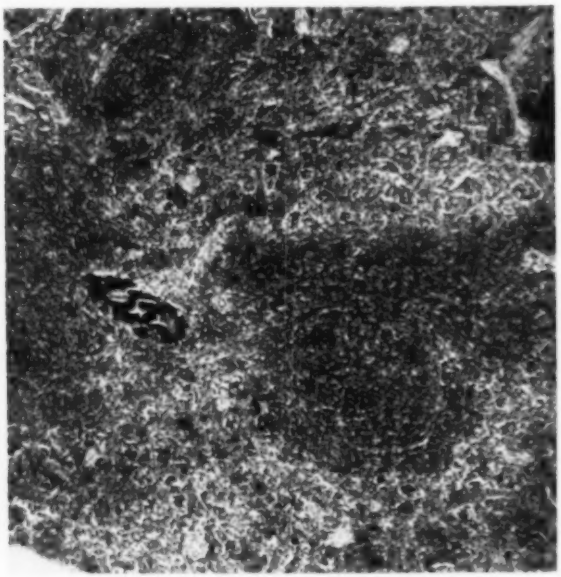

FIGURE 3: Spleen of a guinea pig treated with neomycin for 77 days starting 21 days after infection with virulent tubercle bacilli. There remains only a healed calcified area (x64).

Histopathologic Studies: The microscopic examination provided additional evidence of the specific therapeutic potential of neomycin. In direct contrast to the extensive necrotizing lesions seen in the parenchymal organs of the untreated animals (fig. 2) there was relatively little evidence of active tuberculous disease in the animals treated with neomycin. There was no histologic evidence of tuberculosis in sections from the lungs. Five of the animals had histologically normal spleens and in 5 others the spleen contained small inactive fibrotic or calcified areas as shown in figure 3. However, there were in the livers of 5 animals treated with neomycin small but definitely active tuberculous foci. In all but 2, the site of inoculation and axillary lymph nodes had persistent regions of necrosis.

With the exception of the single animal noted previously, the animals treated with 6 mg. of streptomycin daily had microscopic evidence of regressive changes and healing that was superior to the result achieved by the administration of neomycin. None had

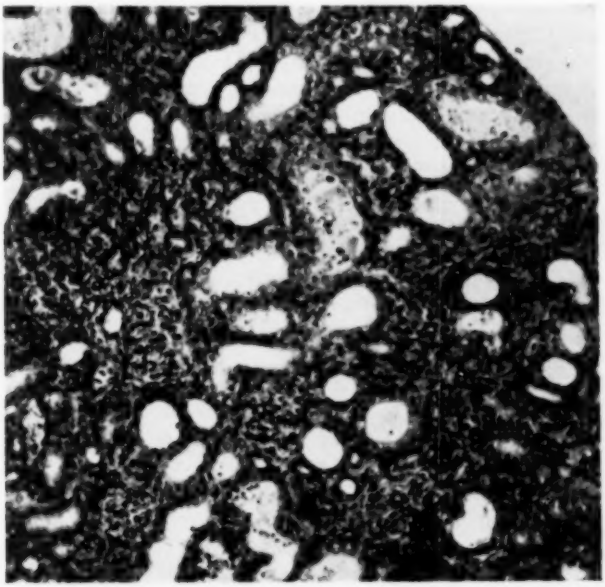

FIGURE 4: Cortex of kidney of a guinea pig treated with neomycin for 77 days. There is degeneration of the proximal tubules with cellular infiltrate consisting of lymphocytes, macrophages and proliferating fibrocytes. The glomerular involvement may be secondary to the interstitial change. The distention of the tubules appeared to be greater in this section than was generally true of kidneys from most of the other guinea pigs treated with neomycin.

any evidence of residual activity at the site of inoculation and only one had histologically evident tuberculous changes in an axillary lymph node. None had active foci detectable in the liver.

An average index of infection based on histopathologic characteristics of the disease in each animal is presented in table 2. By this method values ranging from 10 to 35, depending on the extent of involvement, are given to each organ with histologic evidence of actively progressive lesions. Values of 1 to 3 are ascribed when there is microscopic evidence of regression and healing such as fibrosis or calcification. Referring to table 2 it is seen that, with respect to the lungs and the spleens, the degree of regression and healing of the previously active disease is about the same for the groups treated with neomycin and with streptomycin. However, the greater index of infection recorded for the group treated with neomycin is due to the failure of healing of the site of inoculation and to the persistence of small but active foci in the livers of some of the animals.

Renal Lesions: The kidneys from the guinea pigs treated with neomycin had small scattered regions in the cortex which, under low power, resembled focal interstitial nephritis. These were found to be regions of tubular degeneration and cellular infiltration as presented in figure 4. Glomeruli immediately within such regions appeared to be compressed but they were not involved by the cellular infiltrate. In some sections the tubules immediately adjacent to these foci were distended as shown in figure 4, but in general the rest of the cortex was morphologically normal. It was estimated that these focal lesions occupied about 10 to 25 per cent of the area of the cortex in each section. There was no comparable alteration in the structure of the renal cortex in sections from the untreated animals or from those treated with streptomycin.

Comment

In order to detect any beneficial effect of a new material in experimental tuberculosis it is necessary that the drug be administered in the maximal tolerated amounts. In this experiment we were primarily concerned with the therapeutic properties of neomycin and gave consideration to its toxic effects only as it might limit the amount of drug that could be given to each animal. It was originally planned to increase the daily dose of neomycin until the upper limits of tolerance were reached as determined by maintenance of body weight. However, the dose was not increased above 8,000 units twice daily even though this much did not appear to be prejudicial to the life of the animals as judged by maintenance of body weight. This dose is equivalent to 125 mg.

of neomycin sulfate per kilogram of body weight per day. It was felt that if the drug had little or no deterrent action on the disease at this high dosage further work would not be indicated. The results, however, are sufficiently encouraging to warrant further studies designed to establish the optimal therapeutic dose and the optimal frequency of administration of neomycin in experimental tuberculosis of guinea pigs.

The limit of the usefulness of neomycin in the treatment of tuberculosis will be guided by its toxicity. Further studies are required to determine whether the renal lesions seen here were due to the high doses used and whether the optimal therapeutic dose for guinea pigs is low enough to preclude serious renal damage. Of particular interest are the preliminary observations in an experiment still in progress that neomycin is as effective against experimental infection due to streptomycin-resistant tubercle bacilli as against streptomycin-sensitive infection.

SUMMARY AND CONCLUSIONS

Twenty-one days after infection with virulent human tubercle bacilli 10 guinea pigs were started on treatment with neomycin as follows: 2,000 units twice daily for 6 days, 4,000 units twice daily for 20 days, 6,000 units twice daily for 24 days and finally 8,000 units twice daily for 27 days for a total of 77 days of treatment. Six other animals similarly infected were treated with 6 mg. of streptomycin daily for 77 days and 10 untreated animals served as controls. When all the animals, including the controls, were killed after the treatment period there was found to be very little grossly evident disease in the animals treated with streptomycin and in those treated with neomycin in contrast to the extensive tuberculous involvement in the untreated animals. Microscopic evidence of healing such as fibrosis and calcification in tissues from the animals treated with neomycin indicated that this antibiotic was capable of effecting a reversal of the progressive tuberculosis that was present when treatment started. The effect of neomycin was not as great as that produced by streptomycin in the doses used. Preliminary observations indicate that neomycin is effective against experimental infections due to streptomycin-resistant tubercle bacilli. The kidneys from animals treated with neomycin reveal small lesions in the cortex characterized by tubular degeneration and cellular infiltration. The results reported here warrant further study of this antibiotic.

SUMARIO Y CONCLUSIONES

Veintiun dias después de haber sido infectados con bacilo tuberculoso de tipo humano, diez cuyes fueron tratados con neomycin

como sigue: 2,000 unidades dos veces al día durante seis dias; 4,000 unidades dos veces al día durante veinte dias; 6,000 unidades dos veces al día durante veinticuatro dias y finalmente 8,000 unidades dos veces al día durante veintisiete dias, para completar un total de 77 dias de tratamiento. Otros seis animales, igualmente infectados fueron tratados con 6 mg. de estreptomicina diariamente durante 77 dias. Diez animales no fueron tratados para servir como testigos. Cuando los animales, incluyendo los controles, fueron sacrificados, se encontró muy ligera evidencia macroscópica de infección en aquellos tratados con estreptomicina y neomycin, contrastando con el extenso ataque tuberculoso de los animales testigos. Signos microscópicos de curación tales como fibrosis y calcificación encontrados en los animales tratados con neomycin, indican que este antibiótico fué capaz de detener y curar la tuberculosis progresiva existente en ellos al ser iniciado el tratamiento. El efecto producido por la neomycin no fué tan grande como aquel producido por la estreptomicina en las dosis usadas. Observaciones preliminares indican que la neomycin es efectiva en contra de la infección experimental por bacilo tuberculoso estreptomicina-resistente. Los riñones de los animales tratados con neomycin mostraron pequeñas lesiones corticales caracterizadas por degeneración tubular en infiltración celular. Los resultados aquí reportados indican la conveniencia de continuar el estudio de este antibiotico.

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Bed Rest, Collapse, and Streptomycin in the Treatment of Pulmonary Tuberculosis*

II. Toxicity Studies, and Observations on Streptomycin Sensitivity

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In a previous article[1] the results obtained by treating 77 cases of pulmonary tuberculosis with bed rest, various collapse measures, and streptomycin were discussed.

This communication summarizes the toxic manifestations which were encountered; and describes the results of streptomycin sensitivity tests which were made on the tubercle bacilli cultured from the sputum or gastric contents following a course of streptomycin therapy.

Methods

The following clinical and laboratory examinations were made on 31 patients before and after receiving a course of one gram of streptomycin daily for six weeks. The patients were questioned about dizziness, headache, diplopia, flushing, etc. They were examined at intervals for skin rashes and positive Romberg signs. The blood non-protein nitrogen was determined; the urine was tested for albumin, and the centrifuged sediment examined microscopically; audiograms were plotted; and the response of the vestibular apparatus to caloric stimulation was determined.

Sensitivity tests done by one of us (W.F.) on the first 43 determinations utilized the liquid media method as described by Canada, et al.[2] The last 18 determinations were done by another of us (B.J.W.) using solid media as described by Karlson and Needham.[3] An identical technique was followed in all instances using the following concentrations of streptomycin per cubic centimeter of media: Control, 1.0 micrograms, 10.0 micrograms, 20.0

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The opinions expressed herein are those of the authors and do not necessarily represent those of the Medical Department of the Navy or of the Naval Service at large.

micrograms, 100 micrograms, and 1000 micrograms. In none of the determinations was "Tween 80" used to enhance bacterial growth.

Results

Serious toxic reactions were not encountered.[4-6] The clinical examinations revealed occasional mild manifestations of drug toxicity, but nothing severe was noted. The blood non-protein nitrogen did not exceed normal limits. Albuminuria and abnormal urinary sediments were not noted. The audiograms of five cases revealed slight loss of hearing in the higher frequencies, and the response to caloric vestibular stimulation was abnormal in two cases. Two additional cases complained of dizziness, but audiograms and caloric tests did not give objective evidence of eighth nerve damage.

In Chart 1 the *in vitro* sensitivity and resistance of the tubercle bacilli isolated from the sputum and gastric contents of 61 cases of pulmonary tuberculosis treated with streptomycin is plotted according to dosage and duration of treatment. The organisms are considered sensitive if the growth in liquid media is definitely inhibited by concentrations of 10 micrograms or less of streptomycin per cubic centimeter.

While this group of cases was being studied it was noted that a large proportion of the streptomycin resistant cultures were obtained from cases which persistently excreted large quantities of tubercle bacilli. This was indicated by the consistent presence of strongly positive concentrates and was usually associated with either poor therapeutic results or with persistent cavitation. Conversely it was noted that occasional positive cultures which came as a surprise after a period of seemingly successful therapy with sputum conversions were frequently streptomycin sensitive. In Chart 2 an effort is made to objectively evaluate these impressions by comparing the relationship between the streptomycin sensitivity of the excreted bacilli and: (a) the anatomic extent of the lesions

CHART 1

Relationship Between Streptomycin Sensitivity Determination, Dosage of Streptomycin and Duration of Treatment.

	S	R	S	R	S	R	S	R	S	R
Weeks of Treatment:	4-7		8-11		12-15		16-20		TOTALS	
Dosage 0.5	4	2			1	1			5	3
In Grams 1.0-1.9	17	7	2	5	6	2	1	6	26	20
Per Day 2.0-4.0		2	2	1	1	1			3	4
TOTALS	21	11	4	6	8	4	1	6	34	27

S: Sensitive to 10 micrograms or less of streptomycin per cc. *in vitro*.
R: Resistant t o10 micrograms or more of streptomycin per cc. *in vitro*.

on the pre-treatment roentgenogram, (b) the presumed pathologic character of the lesions as determined by the history, clinical observation, and examination of serial roentgenograms, and (c) the response obtained with streptomycin therapy. In this last category there were six cases with definite evidence of cavity closure following streptomycin therapy, 20 without evidence of cavitation which nevertheless responded satisfactorily to streptomycin, and 35 with either no evidence of cavity closure or with no improvement of the existing lesions.

Separation of tuberculosis cases into different pathologic types is subject to a great deal of error. In this study the attempt at differentiation was made with no knowledge of the sensitivity tests in an effort to be as objective as possible. Many cases were admittedly borderline and were deliberately put into one group or the other depending upon which type of disease seemed predominant.

Our attempt to study the relationship between streptomycin sensitivity and the type of disease being treated as recorded in Chart 2 seemingly adds confirmation to the work of Howard, et al,[7] and Howlett, et al[8] which indicates that the pathologic character of the disease process and the response of this disease to treatment has a bearing upon the tendency for drug resistant strains to emerge. It must be remembered that for a sensitivity determination to be made it is necessary that the sputum remain positive following a course of therapy. Thus, those cases in which the sputum converted from positive to negative, and therefore in which the best therapeutic results were obtained, could not be evaluated. It may be that the organisms present in an individual

CHART 2

Relationship Between Streptomycin Sensitivity Determination, Response to Therapy and Anatomic Extent of Disease being Treated.

		Sensitive*	Resistant**
Response to Streptomycin Therapy	Good		
	With Cavity Closure	6	0
	Without Evidence of Cavity	15	5
	Poor	13	22
Pathologic Type of Disease	Exudative and/or Caseous-pneumonic	24	9
	Fibro-productive and/or Fibro-cavernous	10	18
Anatomic Extent of Disease	Moderately Advanced	6	6
	Far Advanced	28	21

*Sensitive to 10 micrograms or less of streptomycin per cc. *in vitro*.
**Resistant to 10 micrograms or more of streptomycin per cc. *in vitro*.

with sputum conversion are even more likely to remain streptomycin sensitive than the organisms in the cases which responded favorably. If this be true the data in Chart 2 would become even more conclusive.

Serial determinations of the streptomycin sensitivity were done on five cases whose sputum remained positive during prolonged periods of treatment. In each case the organisms eventually became resistant and it was noted that this property developed rapidly, i.e. the organisms which had remained sensitive to 20 micrograms or less of the drug per cubic centimeter for six to eight weeks would suddenly become resistant and grow well in concentrations of one thousand micrograms per cubic centimeter after eight to ten weeks of treatment.

Several cases have been given one course of streptomycin therapy and because of subsequent developments received a second course of the drug. If the organisms were sensitive to 20 micrograms or less of streptomycin following the first course of treatment, there was always a clinical response (i.e. a decrease in fever, pulse rate, cough, sputum, etc.) which indicated that the organisms were probably sensitive to the drug *in vivo*. This observation requires cautious evaluation because animal experimentation indicates that the critical value is nearer an *in vitro* sensitivity determination of 10 micrograms of streptomycin per cc.[9]

Discussion

It is evident from Chart 1 that a considerable number of tuberculous individuals who remain sputum positive following a course of streptomycin therapy are likely to excrete drug fast tubercle bacilli. These drug fast strains emerge in sufficiently great numbers to indicate that they are the predominant strain being excreted and therefore probably also predominate within the tuberculous lesions from which they were derived. This tendency for the bacilli to become streptomycin resistant manifests itself whether small amounts of the drug are given for brief periods or large doses for prolonged periods. This is not to say that there is no more tendency for resistant strains to emerge as the period of treatment is prolonged. The essential point is that even brief courses of therapy frequently result in the emergence to dominance of drug resistant strains.

The tendency for tubercle bacilli to develop resistance to streptomycin *in vitro*, and probably *in vivo*, imposes a responsibility on the physician who prescribes it for the treatment of pulmonary tuberculosis. There is no assurance in any given case once streptomycin has been used that it can ever be used again effectively since its administration may render the excreted organisms drug

resistant. Thereby patients may be deprived of the beneficial effects of streptomycin therapy at a time when it is urgently indicated. This would seem especially true in cases with lesions of a chronic (fibro-productive or fibro-cavernous) type, or in cases in which cavity closure or definite improvement in the lesions cannot be reasonably expected during the period of therapy.

The results of a streptomycin sensitivity test are not known until about eight weeks after the sputum or gastric contents have been cultured. Thus, the information given by the test is not available when it is most needed. This is a disadvantage, and it is hoped that the rapid culture method of Berry and Lowry[10] may meet this need. However, this delay does not in any way diminish the necessity for determining the sensitivity following a course of streptomycin therapy. If streptomycin is to be used alone, or in conjunction with other methods of treatment such as pulmonary collapse or excisional surgery, the sensitivity of the patient's organisms *must* be known before a second course of streptomycin therapy is begun. Otherwise the drug should not be used, because if the organisms are resistant the drug is actually not being used. By the same token, knowledge that streptomycin can or cannot be used effectively in a given case, may very well alter a proposed therapeutic regimen. This is especially likely when excisional surgery is planned because the results of lobectomy or pneumonectomy are much better when accompanied by streptomycin therapy than in its absence.[11]

SUMMARY AND CONCLUSIONS

1) The toxicity of streptomycin was investigated in 31 cases of pulmonary tuberculosis which received one gram of the drug daily for six weeks and was found to be negligible.

2) The *in vitro* determination of the streptomycin sensitivity of tubercle bacilli cultured from the sputum or gastric contents of 61 cases of pulmonary tuberculosis was determined after terminating a course of streptomycin.

3) A definite tendency for the bacilli to develop *in vitro* and probably *in vivo* resistance to the drug was noted regardless of the dosage or the duration of therapy.

4) The type of disease being treated and the response observed following streptomycin treatment has been shown to influence the tendency for streptomycin resistant strains of tubercle bacilli to emerge.

5) The decision to administer streptomycin to a case of tuberculosis should be made with due regard for the type of lesion being treated and with the realization that one course of therapy may deprive the patient of the beneficial effect of the durg at a later date.

RESUMEN

1) Se ha investigado la toxicidad de la estreptomicina en 31 casos de tuberculosis pulmonar que recibieron un gramo de la droga durante seis semanas y esa toxicidad se encontró sin importancia.

2) Se determinó *in vitro* la sensibilidad del bacilo de la tuberculosis del cultivo de esputos o del contenido gástrico en 61 casos de tuberculosis pulmonar después de terminarse la serie de estreptomicina.

3) Se notó una clara tendencia del bacilo a desarrollar resistencia a la droga *in vitro* y probablemente *in vivo* sin que influya la dosis o la duración del tratamiento.

4) La forma de la enfermedad y la respuesta observada después de tratarse con estreptomicina ha mostrado que influyen en la tendencia a aparecer bacilos resistentes.

5) La determinación de emplear la estreptomicina en un caso dado debe tomarse considerando debidamente el tipo de lesión por tratar y dándose cuenta de que una serie de este tratamiento priva para el futuro al enfermo de la acción benéfica que podría necesitarse en el futuro.

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A Clinical Appraisal of the Value of Para-Aminosalicylic Acid With and Without Streptomycin in the Treatment of Tuberculosis

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The purpose of this report is to present our experience with 30 tuberculous patients in whom para-aminosalicylic acid (PAS), was used either as the sole therapeutic agent or in combination with or following a course of streptomycin. The study was essentially clinical and the conclusions were drawn from the response of the temperature, the blood picture, the sedimentation rate, the roentgenologic changes and the general well being of the patient. Toxic effects were gauged by weekly blood counts, urine analyses, liver function tests (thymol turbidity and cephalin flocculation), prothrombin time and evaluation of symptoms indicative of toxicity.

The study was begun in January 1948 and, except for two patients, all had completed their course of therapy as of March 1949. The shortest period of treatment in the completed cases was 34 days; the longest 171 days; and the average 87.4 days. The drug was discontinued when maximum effects or failure to obtain results were noted by the above mentioned criteria. Our policy is to begin with 6 gms. daily in four divided doses and increase the dose to 9 gms. within a few days if the patient tolerates the drug. Larger doses are cumbersome to administer because of the large number of capsules the patient has to consume and frequently cause gastric distress. Those who respond favorably seem to do so with the smaller doses. In combination with streptomycin or other antibiotics, the reports in the literature appear to confirm our observations that the doses we used are adequate. The smallest total dose administered was 297 gms.; the largest 1288 gms.; and the average 683.4 gms.

We were not equipped to do bacterial sensitivity studies nor blood level determinations. Reported observations indicate that

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levels of 7 to 11 mgm. per 100 cc. of blood are obtainable by the doses we gave. In combination with streptomycin there seems to be general agreement that 5 to 6 gms. daily are sufficient.

The therapeutic effectiveness of PAS was judged by the favorable response after a fair trial of bedrest failed in the patients in whom it was the only antibiotic used and by the additive effect in the patients who had obtained maximum benefits from or had become resistant to, streptomycin.

Early in the study it became evident from reported experimental and clinical observations that PAS is not as effective as streptomycin and that it showed more promise as an adjunct to the latter. It is not surprising, therefore, to note in Table 1 that PAS alone was utilized in only five cases. Of the 18 cases in which improvement was recorded (Table 3), two were contributed by this group. Of the five patients, two presented bilateral disseminated, exudative tuberculosis which contraindicated a trial period of bedrest—neither one improved with PAS. In the remaining three cases recent exacerbation of existing disease took place on bedrest; two showed clinical improvement after the drug was introduced.

TABLE 1

Cases Treated with PAS alone or in Combination with Streptomycin.

PAS Alone	PAS and Streptomycin Concurrently	PAS and Streptomycin Alternately
5	12[A]	13[B]

A—Average Interval between beginning of PAS and streptomycin 4.6 weeks—One case not considered in the evaluation for reasons mentioned in text.

B—Average Interval between discontinuance of streptomycin and beginning of PAS—22.5 weeks.

In 25 patients (Table 1) PAS was used in conjunction with streptomycin. One of these cannot be included in the evaluation since the combined drugs were employed as a "protection" in a pneumonectomy for an ineffective thoracoplasty. It will be noted that an average interval of 4.6 weeks elapsed between the beginning of streptomycin and the introduction of PAS when the antibiotics were used concurrently. In only one instance were the two drugs administered simultaneously. The shortest interval was one week and the longest 15 weeks. PAS was administered only after the intervals mentioned revealed no effect, or not as adequate a response as was anticipated in similar cases from previous experience with streptomycin, or maximum benefit. Of the 11

patients in this group eight or 72.7 per cent showed additional clinical or clinical and roentgenographic improvement.

Thirteen patients received PAS after streptomycin had been discontinued. Eight of them had had 30 to 60 gms. of streptomycin with no effect; the remainder were streptomycin resistant after having received from 90 to 120 gms. of the drug. The shortest interval between discontinuance of streptomycin and the beginning of PAS was one week; the longest one year; with an average of 22.5 weeks. Excluding the three cases in which PAS was introduced one year after completion of streptomycin therapy, the average interval was 12 weeks. Clinical or clinical and roentgenographic improvement was observed in eight patients or 61.6 per cent. I should like to stress that not only is the ratio of improved cases smaller in this series but also the fact that roentgenographic resolution was not as striking nor as rapid as in the group which received PAS and streptomycin concurrently.

TABLE 2

Classification of Treated Cases*

Tuberculous Pneumonia or Bronchopneumonia	Recent Spread or Reactivation	Extrapulmonary Tuberculosis
14[A]	12	1

*In one case—PAS and streptomycin were used just prior, during and for 2 weeks following pneumonectomy for ineffective thoracoplasty; evaluation is not possible.

A—Two patients also had tuberculous lymphadenitis and one of these tuberculosis of the chest wall.

Table 2 shows the distribution of the cases according to the type of tuberculosis. It will be seen that of the 29 who had pulmonary tuberculosis, 28 had exudative disease. In the 14 patients who presented recent spread or reactivation, the older lesion was not affected when improvement in the more recent process took place. This observation is more or less universal among those who have had experience with PAS. It is interesting to note, although of no significance in view of the small number of cases, that the one patient with intestinal tuberculosis and the two who had tuberculous lymphadenitis were not benefited.

It has been repeatedly stressed that streptomycin does not replace therapeutic measures which have proved their value over a long period of time. This should be said even more emphatically of PAS which is a less effective drug. Table 3 substantiates what has just been said even when combined therapy is used. Only two of the 18 patients who improved were discharged well requiring

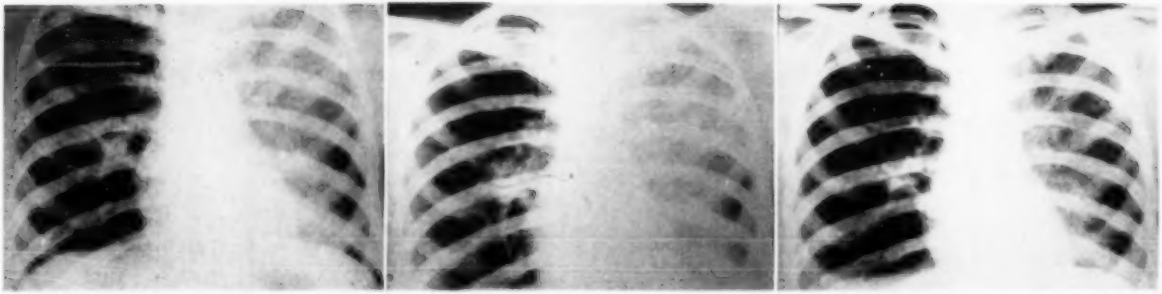

FIGURE 1 (CASE 1) FIGURE 2 (CASE 1) FIGURE 3 (CASE 1)

Figure 1 (Case 1): K.A., white female, aged 19 years. Admitted 5-8-48 and discharged 1-7-49. X-ray (5-18-48) prior to the introduction of streptomycin reveals a tuberculous pneumonia of the left lung and disseminated minimal exudative infiltrate right midlung region.—*Figure 2 (Case 1):* After 44 gms. of streptomycin and prior to PAS. X-ray (6-30-48). Note progression of pneumonia in left lung. No clinical improvement or reduction in fever.—*Figure 3 (Case 1):* After 28 days of combined therapy. Seventy-three gms. of streptomycin and 178 gms. of PAS. X-ray (7-28-48). Note appreciable resolution bilaterally.

TABLE 3

Clinical and Roentgenographic Response to PAS with or without Streptomycin.

Improvement	Clinical and Roentgenographic Improvement	Unimproved
4[A]	14[B]	11[C]

A—Two patients have undergone thoracoplasty with improvement.
One is receiving pneumothorax on one side.
One recently had a cavernostomy.

B—Two patients have had relapse since discontinuance of PAS.
Two have been discharged as partly arrested.
Two patients have undergone successful thoracoplasty.
One patient has had a lobectomy.
One patient is awaiting lobectomy.

C—One patient has expired.

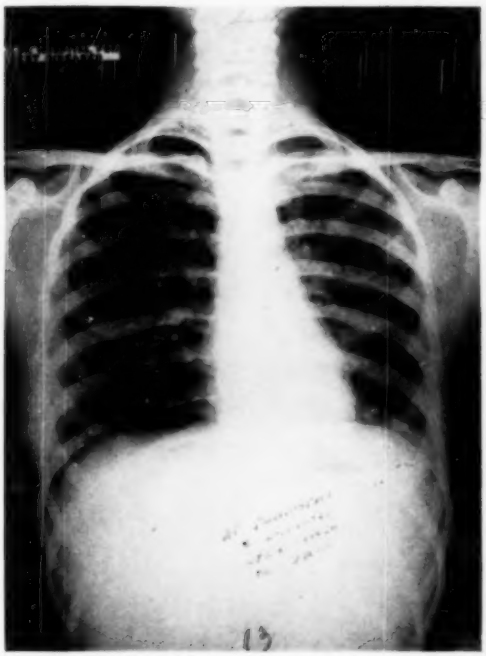

FIGURE 4 (CASE 1): After 100 gms. of streptomycin and 376 gms. of PAS. Both drugs discontinued 8-30-48, five days after above film was taken. She has been well since discharge and has retained the residual productive process shown above.

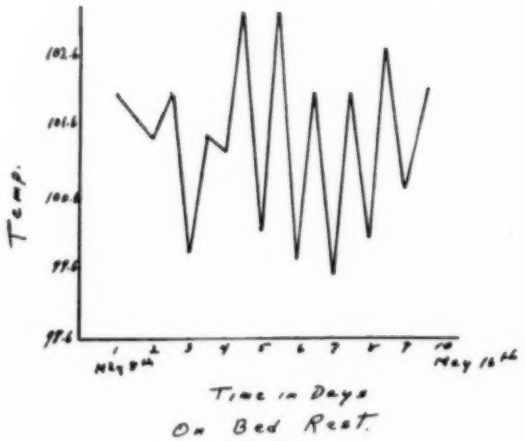

FIGURE 5 (CASE 1)
Temperature curve prior to streptomycin.

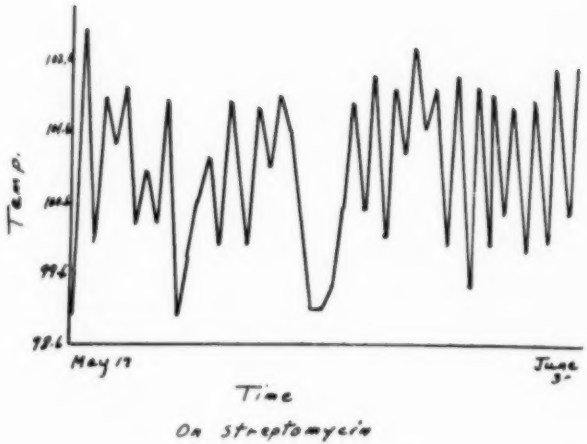

FIGURE 6 (CASE 1)
Temperature graph during streptomycin therapy.

no additional therapy other than bedrest. Seven others have undergone surgery and one is awaiting lobectomy. Two have relapsed after initial improvement and the prognosis in both is grave. The remainder are continuing on bedrest and the outlook for at least three for formative collapse therapy in the future appears good.

A collateral observation made in the weekly blood counts for toxic effects was the change in the total and differential white blood count, in roughly 34 per cent of the improved cases. It was

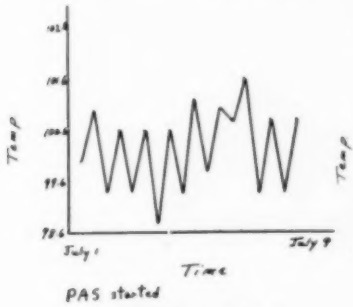

FIGURE 7 (CASE 1)
Temperature record at beginning of PAS.

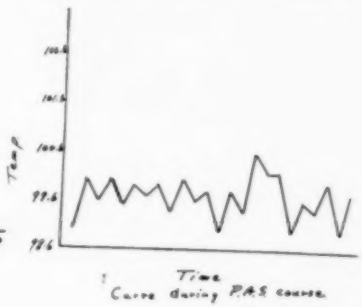

FIGURE 8 (CASE 1)
Temperature curve after PAS.

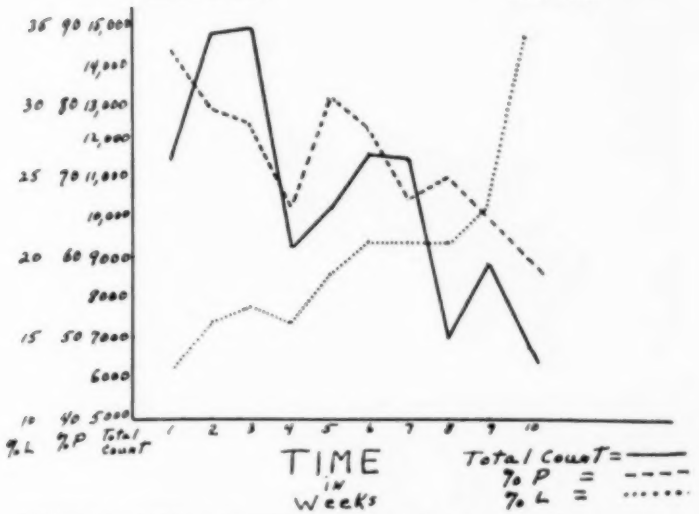

FIGURE 9 (CASE 1): Hemogram. Note decline in total white count and polymorphonuclears and increase in lymphocytes after the introduction of combined antibiotic therapy.

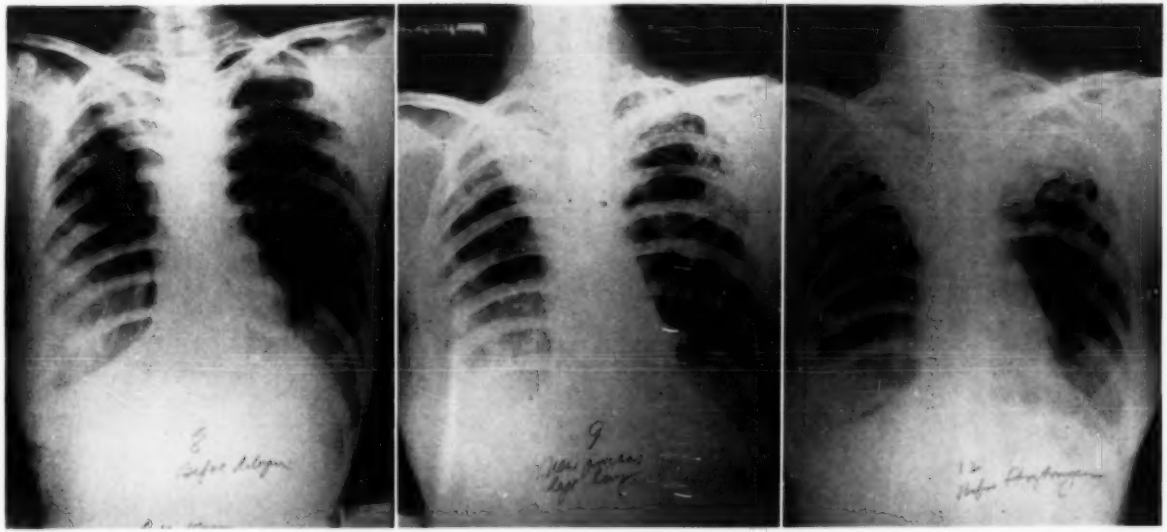

FIGURE 1 (CASE 2) FIGURE 2 (CASE 2) FIGURE 3 (CASE 3)

Figure 1 (Case 2): D.C., white female, aged 42 years. X-ray (12-44) prior to relapse showing fibrous tuberculous right upper and fibro-calcific disease left upper, thickened mediastinal and parietal pleura, right side and bilateral emphysema.—*Figure 2 (Case 2):* February 1945, when relapse took place. Note new infiltrate in left 2nd and 3rd anterior interspaces and cavity formation in 1st interspace.—*Figure 3 (Case 2):* September 1947. Note progression of disease in the left lung despite bedrest. Above film taken just before introduction of streptomycin.

interesting to note reduction in leukocytosis or return to a normal count, decline in the polymorphonuclears and a rise in the lymphocytes. Lowering of the sedimentation rate frequently followed the improvement in the blood picture but neither was constant and as Table 4 shows no hematologic response occurred in about 30 per cent of the patients who improved.

TABLE 4

Effect of PAS on Blood Picture.

Favorable Hematologic Response	No Hematologic Response
11[A]	13[B]

A—One of these was not improved by PAS.

B—In 6 patients who showed both clinical and roentgenographic improvement. In 2 patients who showed only clinical improvement.

As for toxic effects it should be said that we do not consider nausea, which was usually transient, a serious problem even though it was a frequent observation. In no instance did we have to discontinue the drug because of this complaint. One patient developed leukopenia with granulocytopenia after 144 gms. of PAS was administered. The antibiotic was discontinued for one week and then resumed without untoward effects. No other toxic hematologic changes were encountered. Even though we performed frequent liver function tests, prothrombin time determinations and urine analyses, evidence of liver or kidney damage was not encountered.

The following cases are presented in detail as representative of the material reflected in the four tables shown above.

Case 1: K.A., white female, aged 19 years who was admitted to the hospital May 8, 1948 and discharged January 7, 1949. She had been followed as a contact since 1935 when her mother died of pulmonary tuberculosis. One month prior to admission she was taken with chills, fever, nonproductive cough and chest pain which was aggravated by breathing. Her physician hospitalized her for pneumonia and prescribed penicillin. A positive sputum, however, was obtained and she was transferred to the chest hospital where positive sputum was confirmed and x-ray inspection showed evidence of disease in the left lung. Streptomycin 1 gm. daily was instituted on May 17th after nine days of bedrest during which time the fever was not affected and the general condition of the patient failed to improve. Between May 17th and June 30th, 44 gms. of streptomycin were administered with no improvement. On July first PAS was commenced and from this time until August 30th both this and streptomycin were continued with noticeable favorable changes clinically and roentgenographically. Her temperature progressively declined to within normal

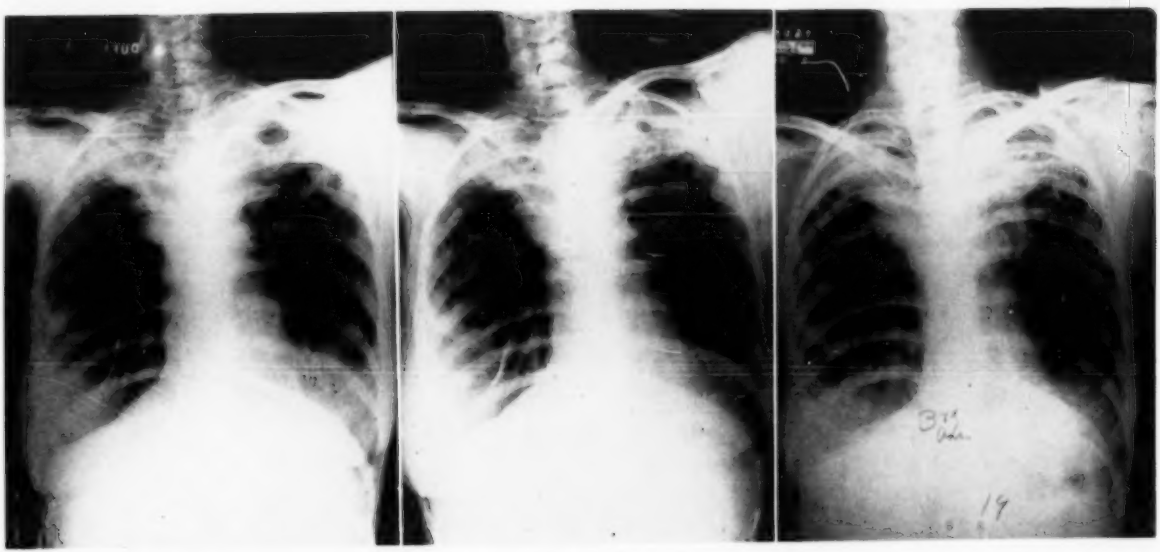

FIGURE 4 (CASE 2) FIGURE 5 (CASE 2) FIGURE 6 (CASE 2)

Figure 4 (Case 2): Lordotic film showing cavity in left upper lobe at beginning of streptomycin.—*Figure 5 (Case 2):* Lordotic film after 130 gms. of streptomycin. Note marked reduction in size of cavity and partial resolution of infiltrate below level of shrunken upper lobe.—*Figure 6 (Case 2):* September 1948, on readmission to the hospital and after final discontinuance of streptomycin. Note reinflation of cavity in left upper lobe and recurrence of inifiltrate below the level of shrunken upper lobe.

limits, the pneumonic process gradually resorbed as revealed by serial roentgenograms and the total white count and the polymorphonuclear cells dropped while the lymphocytes rose as shown in the graph. She received a total dosage of 376 gms. of PAS and 100 gms. of streptomycin when both drugs were discontinued August 30th. Her weight increased above the normal for her height and age and her condition so improved that she was discharged January 7, 1949 to continue out-patient observation. (Shown is a series o x-ray reproductions of the chest and graphs of the temperature curve and the changes in the blood picture).

Case 2: D.C., 42 year old white female admitted to the hospital for the first time on April 17, 1939 with a history of pulmonary tuberculosis dating back to 1927. The sputum was positive and the x-ray of the chest revealed bilateral fibro-calcific disease of the upper lung fields and a cavity in the right apex. Right pneumothorax was induced April 18, 1939 and became effective July 2, 1939. She was discharged and continued to receive pneumothorax refills until December 1942, when the lung was re-expanded. She did well until February 1945 when cough, expectoration and hemoptysis returned. Sputum was again found to contain tubercle bacilli and the x-ray film showed evidence of recent infiltrate in the left upper lobe with cavity formation. She remained on bedrest until February 1946 when she was admitted to the hospital for the induction of pneumothorax on the left side. This procedure was attempted but after several refills abandoned because of adhesions. She continued on bedrest but because she failed to improve streptomycin was introduced in September 1947. By January 1948 she had shown appreciable improvement, with negative sputum and the cavity in the left upper lobe had

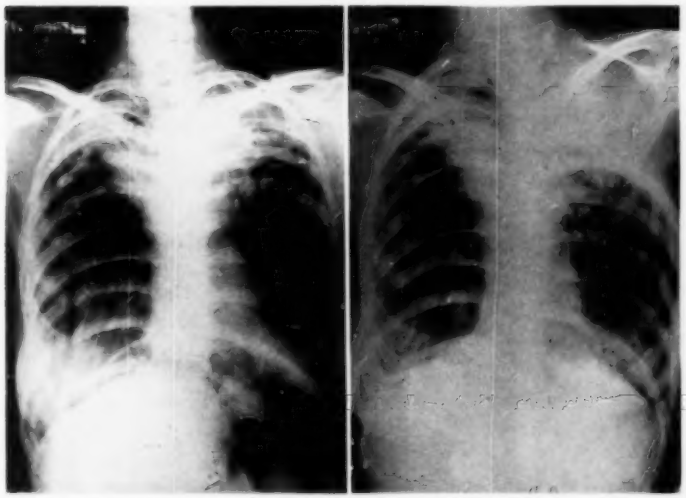

FIGURE 7 (CASE 2) FIGURE 8 (CASE 2)

Figure 7 (Case 2): After 3 months of PAS. Note no change in lesion despite clinical improvement.—*Figure 8 (Case 2):* After 2 stage left thoracoplasty. Cavity closed, sputum negative and general condition improved.

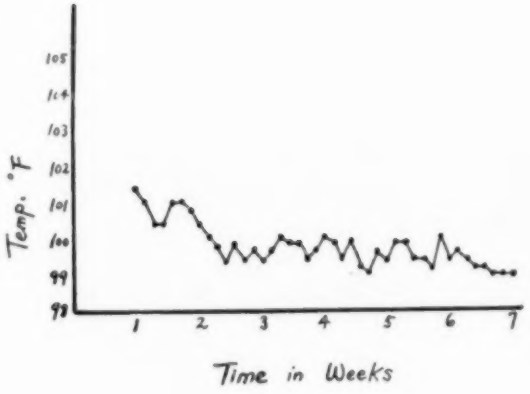

FIGURE 9 (CASE 2)
Note reduction in fever after PAS therapy.

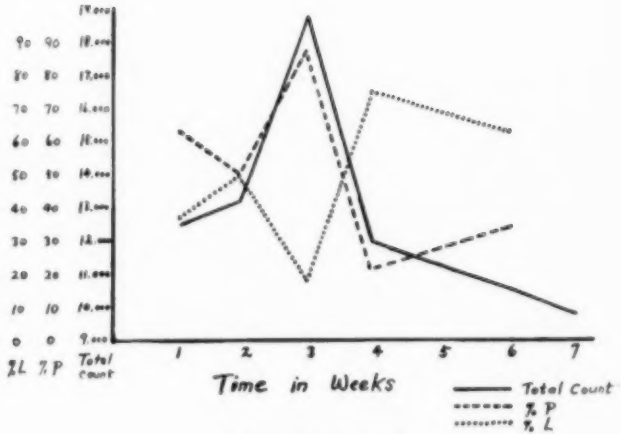

FIGURE 10 (Case 2)
Hemogram showing favorable response after PAS therapy.

almost disappeared. By this time she had received 80 gms. of streptomycin. About three weeks after streptomycin was discontinued she had a relapse and the drug was reinstituted. Again she showed improvement and by April 1948 a total of 130 gms. of streptomycin had been administered. The drug was again discontinued and once more symptoms returned. On September 13, 1948 she was readmitted to the hospital for PAS therapy. The temperature returned to normal limits within three weeks, cough and expectoration were materially reduced, sputum again became negative and her general well being was improved. The roentgenograms of the chest however, revealed persistence of cavitation and for this reason pneumoperitoneum was induced but failed to effect the cavity. The PAS was continued until January 1949 when she had a two stage thoracoplasty. Although there was no roentgenographic improvement, clinically she benefited from the drug. The graph shows the favorable effect on the blood picture as evidenced by reduction in the total white count and polymorphonuclears and the rise in the lymphocytes. (See graphs and x-ray reproductions accompanying this case).

Case 3: B.M., colored female, 25 years of age, admitted November 3, 1947 and expired June 7, 1948. She was well until October 1947 when she developed a cold characterized by cough which gradually became productive, night sweats and fever. A diagnosis of tuberculosis was made and she was admitted to the hospital. On admission her sputum was positive, she had a moderate fever and the roentgenogram of the chest revealed evidence of disease in the left lung with scattered foci in the right upper lobe. Streptomycin was instituted on December 12th and continued until January 18, 1948 at which time a total of 38 gms. had been

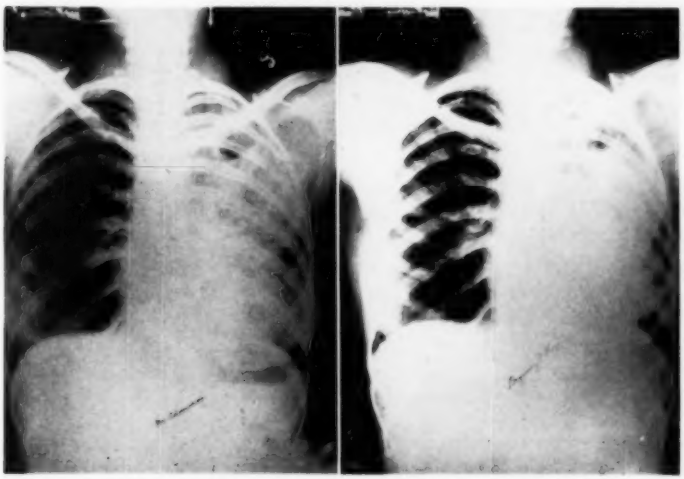

FIGURE 1 (CASE 3) FIGURE 2 (CASE 3)

Figure 1 (Case 3): B.M., colored female, aged 25 years. Admitted November 3, 1947 and expired June 7, 1948. X-ray on admission shows pneumonic cavernous tuberculosis left lung. Moderate disseminated infiltrate right upper lobe.—*Figure 2 (Case 3):* December 12, 1947, when sterptomycin was instituted.

given. The drug had no effect and for this reason PAS was begun on January 27, 1948 and continued until May 12th when it was discontinued after a total of 324 gms. had been given. Roentgenograms of the chest by this time revealed extension of the disease in the right lung and no improvement in the left. Her general condition had deteriorated and her temperature had not altered. On bedrest she grew progressively worse and finally expired June 14, 1948. (See graphs and x-ray reproductions accompanying this case).

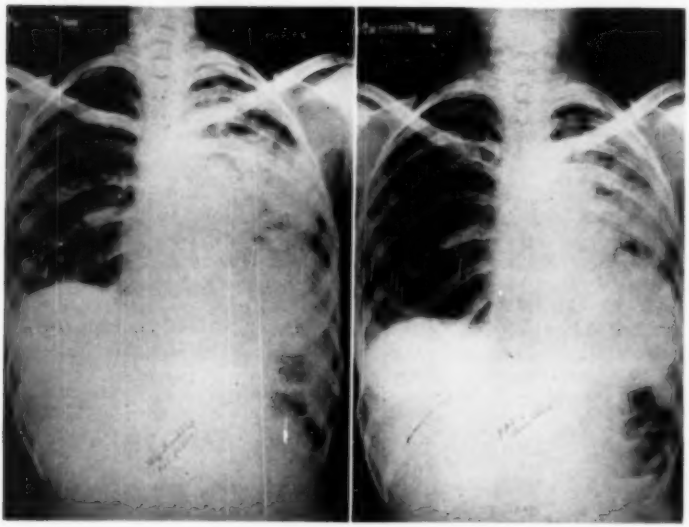

FIGURE 3 (CASE 3) FIGURE 4 (CASE 3)

Figure 3 (Case 3): After 38 gms. of streptomycin. Note increase in disease bilaterally. At this time streptomycin was discontinued and PAS commenced. —*Figure 4 (Case 3):* After 324 gms. of PAS. Note no change in lesion.

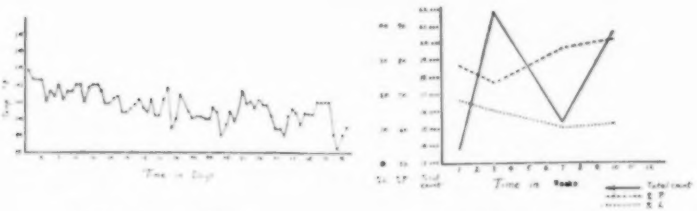

FIGURE 5 (CASE 3) FIGURE 6 (CASE 3)

Figure 5 (Case 3): Temperature curve showing no effect from PAS after a slight initial decline.—*Figure 6 (Case 3):* Hemogram showing continued elevation of total white count and polymorphonuclears and low lymphocyte count.

SUMMARY AND CONCLUSIONS

1) Experience with para-aminosalicylic acid (PAS) is evaluated in 30 patients five of whom received only this drug, 12 concurrently with streptomycin and 13 after streptomycin had been discontinued.

2) The daily dose was 9 gms. in four divided doses. The total dose averaged 683.4 gms.; the smallest being 297 gms. and the largest 1288 gms.

3) PAS is not as effective as streptomycin. Best results are obtained when it is used in conjunction with the latter. Forty per cent of the patients improved who received only PAS, 72.7 per cent when it was utilized in conjunction with streptomycin and 61.6 per cent when it followed the use of streptomycin.

4) Criteria for improvement included changes in clinical picture, serial roentgenograms of the chest, blood counts and sedimentation rates.

5) Toxic effects were judged by frequent liver function tests and hemograms. Transient nausea and one case of transient leukopenia and granulocytopenia were the only toxic effects observed.

RESUMEN Y CONCLUSIONES

1) Se estima la experiencia con 30 enfermos usando PAS. En cinco solo esta droga se usó. En doce en combinación con estreptomicina y en 13 después de usarse la estreptomicina.

2) La dosis diaria fué de 9 gms. La dosis total fué por término medio de 683.4; la más pequeña fué de 297 y la mayor de 1288 gms.

3) PAS no es tan efectivo como la estreptomicina. Los mejores resultados se obtienen cuando se usa en combinación con la última.

Cuarenta por ciento de los enfermos que recibieron solo PAS mejoraron en tanto que usada en combinación con estreptomicina mejoraron 72.7 y el 61.6 por ciento mejoraron cuando se usaron sucesivamente.

4) El criterio para definir la mejoría incluyó el cuadro clínico, la serie de roentgenogramas del tórax, cuentas glubulares y sedimentación.

5) Los efectos tóxicos fueron estudiados por las pruebas funcionales hepáticas y por hemogramas.

Solamente se observó un caso de nausea transitoria, leucopenia pasajera y granulocitopenia en un caso.

Functional Hepatic Impairment in Pulmonary Tuberculosis*

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Introduction

The work presented in this paper has been prompted by the dearth of material on the subject. In a preliminary report of 18 cases by Hurst, Maier and Lough[1] the following observations have been made: That in a study of far advanced pulmonary tuberculosis using Hanger's cephalin cholesterol flocculation test, the Hippuric acid synthesis and the 5 mg. serial Bromsulphalein test as tests of hepatic function, where the NPN, Serum Protein, Cholesterol and Esters, Prothrombin Time, Bilirubin and Urobilinogen were within normal limits, hepatic dysfunction was demonstrated in a large percentage of cases. Bromsulphalein showed the greatest number of positive results—47 per cent.

It will be our object to limit study to what we believe to be two of the most reliable tests of liver function and critically examine the values obtained in the light of the stage of the disease, the chronicity, the amount of inanition present and the character of the pulmonary lesion, always considering other etiological factors which might tend to distort results.

The fact has long been established that hepatic parenchymal damage is a frequent finding at necropsy in the tuberculous. Conflicting opinions have been voiced as to the pathogenesis and the micropathology of the process. Florentin, et al,[2] reviewed 35 cases of chronic pulmonary tuberculosis that came to autopsy and only reported three cases with fatty livers. However, two-thirds of his cases gave evidence of typical inflammatory process without evidence of fatty degeneration. Periportal sclerosis was observed only rarely, but massive proliferation of Kupfer's cells was an almost constant feature. He points out that fat deposition in the liver cells usually starts at the periphery of the hepatic lobule. In order that fat may be deposited, the body must have sufficient reserves in lipids and glucosides, and the endocrine system must be intact. He further reasons that since fatty livers

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may occur in aviators flying at high altitudes or may be induced experimentally in animals by subjecting them to low concentrations of O_2, ever present anoxemia is a possible factor in the development of fatty liver in the individual having sufficient lipoid reserves.

Anoxemia alone however cannot solve this riddle if one recalls the infrequent occurrence of fatty livers in cases of pulmonary emphysema with long standing anoxia. General toxemia and inanition may play an important role. Parini[3] who examined at postmortem the livers of 50 patients with chronic ulcerative intestinal tuberculosis and those of a control series of 50 patients with active tuberculosis without intestinal disease, concluded that in ulcerative intestinal tuberculosis there are always fairly severe fatty changes in the hepatic parenchyma. Characteristically he found these changes involved the peripheral part of the hepatic lobule. Jones and Peck[4] also discussed the extensive fatty infiltration of the liver often associated with extensive tuberculous enteritis. Both these conditions were more apt to occur jointly when mixed or exudative types of pulmonary disease existed. Extreme emaciation appeared to be a constant accompaniment of fatty liver even when enteritis was not present. This finding suggested an underlying metabolic factor such as poor absorption of food from the gastro-intestinal tract due to damage to the intestinal mucosa and increased peristalsis. Vomiting and anorexia similarly might be aggravated by the concommitant exudative disease and the toxemia thereof.

Clinical Material

Fifty-three cases of pulmonary tuberculosis in males were picked at random for this study. With the exception of No. 48 who had a draining empyema of one year's duration, there were no demonstrable tuberculous complications or extrapulmonary lesions. A classification of each case was made at the time of testing according to National Tuberculosis Association standards and a thorough history was taken to rule out other causes of liver damage. Special effort was made to elicit a history of: jaundice, starvation (many patients were refugees from concentration camps), alcoholism, prolonged anesthesia, occupational exposure, and intravenous plasma or whole blood within six months prior to testing. Both the cephalin-cholesterol flocculation test and the bromsulphalein tests were done during the same morning while the patients were in a fasting state. Positive and negative tests were checked periodically by the laboratory against both positive and negative known controls. All negative cephalin-cholesterol flocculation tests where the bromsulfalein retention was over 5 per

cent, were repeated independently. Results were gratifyingly confirmatory in almost every case.

The Studies

It has been shown at necropsy that a pathological diagnosis cannot be predicted on the basis of hepatic function studies alone. One can only interpret positive test findings in terms of the degree of damage to the functional capacity of the organ. F. Mann[5] has emphasized that the various functions of the liver are not injured equally, and thus there is a dissociation of impairment of different liver functions and a corresponding dissociation of the results of the liver function tests. Our choice of two tests, one of which would reflect the active phase of liver damage and the other the residual damage to the parenchyma was made after a review of the recent literature.

The cephalin-cholesterol flocculation test which was chosen as an index of active liver disease has been found to be an extremely valuable test in routine clinical work because of its simplicity and small number of false positive reactions. Sensitivity studies according to Truscott[6] placed cephalin-flocculation first in degree of sensitivity, colloidal gold second, and thymol turbidity third. Moore, Hanger, et al[7] have postulated that a positive flocculation test may be due to an increase in the gamma globulin fraction, a decrease in serum albumin, or a decrease in the flocculation inhibiting property of the albumin.

Following the advice of Hanger[8] a fresh unripened cephalin solution which had remained in the ice box protected from light was used. This emulsion was prepared from the commercial product supplied by Difco Laboratories, Inc. Preparation and laboratory testing was run exactly as described except that the centrifuge tubes were kept in the dark as directed by Neefe and Reinhold.[9] Mateer[10] has shown in a comparison of tests on normal individuals using unripened and ripened cephalin emulsions that if a one plus test with the former is regarded as within normal limits, and positive diagnostic importance is attached only to two, three and four plus tests, that studies with the latter reagent yielded numerous two and three plus false positive results. The unripened cephalin on the other hand, yielded 12.5 per cent of false positives, all of which were only of a one plus magnitude when tested against normal controls. Fresh unripened cephalin has been shown to lack sensitivity and may give negative results where impaired function actually exists. Additional laboratory precautions must and were taken in handling cephalin reagent since exposure to light or air for a protracted period of time will yield numerous two an dthree plus false positives.

A 48 hour reading was employed exclusively despite Saifer's[11] admonition that 48 hour readings yielded a 10 per cent error in the plus one and two range. Our laboratory reactions appeared to be better defined after this period of time and allowance for slight error was made by disregarding all plus one reactions.

Delor and Rheinhart,[12] Lichtman,[13] and Mateer[10] concur that the bromsulphalein test is the most sensitive test of the excretory function of the liver in the non-jaundiced individual. Marginal impairment of function is demonstrated by throwing a large excretory load on the liver.

Mateer, et al[10] studied the bromsulphalein test using the new 5 mg. per kilo dosage. In a study of thirty normal individuals who were subjected to serial sampling of blood following intravenous injection of the dye, the dye had completely disappeared from the blood stream in 73 per cent in 30 minutes, in 86 per cent in 35 minutes, in 96 per cent in 40 minutes, and in 100 per cent in 45 minutes. The normal standard for complete disappearance of the dye after injection has thus been established as 45 minutes when 5 mg. per kilo of dye is used. From the standpoint of economy

TABLE I

Cases Positive to Both Tests

	C.F.	B.S. (per cent)	Stage	Chronicity (years)	Inanition
J.C.	4 plus	12	II	13	0
Lesion: Unilateral Cavitation.					
W.E.	2 plus	6	II	1	0
Lesion: Miliary.					
L.G.	2 plus	7	III	6	3 plus
Lesion: Extensive Bilateral Cavitation.					
T.G.	4 plus	5	II	2	0
Lesion: Bilateral small cavitation.					
H.M.	2 plus	16	II	5	2 plus
Lesion: Bilateral pneumothorax for cavitation.					
J.M.	4 plus	6	III	6	2 plus
Lesion: Bilateral cavitation; healed one side, pneumothorax other.					
A.P.	3 plus	12	III	9	2 plus
Lesion: Endobronchial disease and bilateral cavitation.					
W.S.	2 plus	5	III	2	2 plus
Lesion: Pneumothorax left; thoracoplasty right. Other, Alcoholic. No palpable liver.					

of time and effort, a single 45 minute specimen is satisfactory and was used in this study. The test was performed and evaluated according to the technique and standard laboratory procedure described by Lichtman.[13] Blood bilirubin determinations were done whenever there was a suspicion of bilirubinemia. Precautions were also taken to withdraw the blood sample from the opposite arm from which the dye had been injected. Results were reported in per cent of dye retention, assuming 100 cc. of plasma contained 4 mg. of dye immediately after injection.

Results

A total of 53 cases were studied. Thirty-nine yielded positive cephalin-flocculation reactions, 16 of which were three plus or four plus reactions. Twenty-one cases showe dretention of bromsulphalein after 45 minutes and 10 had retention of 6 per cent or more of the dye. Eight cases were positive to both tests of which only three met the three to four plus and 6 per cent more stringent requirements. See Table 1. Thus 43.4 per cent of all cases studied were positive to the cephalin reagent, 39.6 per cent to the bromsulphalein test and 15.1 per cent to both tests. In other words 34.8 per cent of the patients with positive cephalin-flocculation tests showed bromsulphalein retention and 38.1 per cent positive with bromsulphalein were positive to the cephalin reagent. (Where one of the two tests was highly positive, i.e. 5 per cent bromsulphalein retention or three to four plus cephalin-flocculation and the other was negative, a repeat test was always made).

An attempt to correlate the stage of pulmonary tuberculosis with progressive liver damage yielded these comparable but inconclusive findings. With the cephalin-flocculation test 33.3 per cent of the minimal cases, 44.1 per cent of the moderately advanced cases and 46.2 per cent of the far advanced were positive, while dye retention was evident in 33.3 per cent of the minimals, 38.2 per cent of the moderately advanced, 46.2 per cent of the far advanced cases. Of the cases studied six were classified as stage I, 34 as stage II, and 13 as stage III. The most interesting findings occurred in the group which was positive to both tests; it was unfortunately however, quite small. Here none of the minimal cases furnished positive results while 11.8 per cent (four cases) of moderately advanced disease and 30.8 per cent (four cases) of the far advanced cases were positive to both tests.

It was hoped that a reciprocal relationship might be found between the chronicity of the pulmonary lesion and hepatic parenchymal damage. Our findings definitely ruled out such a relationship. Patients with positive cephalin-flocculation tests

averaged 4.8 years, positive bromsulphaleins 5.3 years, with both tests positive 5.5 years, and with neither test positive 5.2 years.

All patients with inanition in this series were classified as mild, moderate, or severe according to past or present loss of body substance over a protracted period of time. Five of the eight patients who had positive bromsulphalein and cephalin-flocculation tests also had moderate to severe depletion of body substance. Six patients with mild to severe wasting had positive cephalin-flocculation tests. In contrast 10 patients, the majority of whom suffered severe inanition had negative liver function studies. Thus of a group of 31 cases with varying amounts of cachexia, 51.7 per cent had a single positive liver function test, 32.3 per cent were negative to both tests and 16.0 per cent were positive to both tests.

Interpretation of Results

No didactic conclusions can be drawn from these data; certain trends may however be examined and added to the literature on the subject. There appears to be a relatively high incidence of liver disease in patients suffering from tuberculosis. Because of the low incidence of combined positive tests one must assume the presence of more than one type of parenchymal damage and of both active and quiescent disease.

There does not seem to be any correlation between the stage of the pulmonary process and the individual test. In fact the only near conclusion that can be drawn is in the small group of eight cases which were positive to both tests, where there was a definite correlation between stage of disease and liver damage as reflected by the function tests.

We may also assume that inanition per se has little influence over the individual's liver function. But where liver function is found to be impaired using both tests, the chance that cachexia is a factor is better than equal.

Presumption of liver damage was of necessity limited to the liver function tests employed; none of the 53 patients studied had jaundice, hepatomegaly, or other clinical evidence of liver damage. Many had been subjected to surgical procedures without developing complications. Since in our opinion a discrepancy seemed to exist frequently between the test findings and the individual case, an unbiased physician familiar with each case was asked to predict the individual test results basing his opinion upon the extent of the pulmonary lesion, the length of illness with tuberculosis, and the activity of the disease, the latter being defined in terms of symptomatology, interference with nutrition, and toxicity. He was able to prognosticate five cases or 63 per cent of the cases, where both tests were positive, but only 13 or 36 per cent of the

total number of cases for which we had found positive results in one or both of the tests. His predictions thus were no more accurate than a random selection of cases.

SUMMARY

1) Fifty-three cases of pulmonary tuberculosis varying in severity from minimal to far advanced were studied for functional hepatic impairment.

2) Studies were limited to cephalin-flocculation and bromsulphalein tests.

3) Although hepatic dysfunction was demonstrated in a large percentage of cases with a single test, only in a small percentage were both tests positive.

4) In the doubly positive group, correlation with the extent of disease seemed to exist.

5) Inanition per se had little influence over the individual cephalin-flocculation and bromsulphalein tests.

6) It is impossible to predict hepatic damage based upon history and clinical picture in pulmonary tuberculosis.

7) No relationship exists between the chronicity of tuberculosis and hepatic damage.

RESUMEN

1) Se estudiaron cincuenta y tres casos de tuberculosis pulmonar que variaban desde mínima hasta muy avanzada, para determinar la insuficiencia hepática funcional.

2) Los estudios se limitaron al uso de la reacción de la floculación de la cefalina y de la bromosulfaleína.

3) Aunque la disfunción hepática se encontró en gran porcentaje de casos con una sola de las reacciones solo en pequeño porcentaje, fueron ambas reacciones positivas.

4) En el grupo en que fueron ambas positivas pareció existir correlación con el grado de la enfermedad.

5) La inanición por sí sola tuvo poca influencia sobre ambas reacciones.

6) Es imposible predecir el daño hepático basándose en la historia clínica en tuberculosis pulmonar.

7) No hay relación entre la cronicidad de la tuberculosis y el daño hepático.

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Intrathoracic Ganglioneuroma

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Loretz made the first report of an intrathoracic ganglioneuroma in 1870 from an autopsy. Since that time there have been an increasing number of these tumors reported and with the advancement of thoracic surgery in recent years more have been found originating in the mediastinum. A. P. Stout[19] collected 233 neurogenic tumors, of which 62 were located in the mediastinum. He added 10 of his own and one of these was in the chest.

Heuer and Andrus[8] up to 1940, collected 68 intrathoracic ganglioneuromas from the literature. Of these 51 were operated upon with 16 deaths, a mortality of 31 per cent. The deaths were due to shock or hemorrhage at the time of surgery.

This tumor is found mostly in the younger age groups. Stout[19] reported 60 per cent of his series were below the age of 20. Hollingsworth[9] collected 63 cases of intrathoracic tumors of the sympathetic nervous system of which 43 or 68.2 per cent were ganglioneuromas, 48.8 per cent were in children under 10 years of age, while 67.4 per cent were under 20. Heuer and Andrus[8] found 74 per cent under 10 years of age. While two-thirds of these tumors appear under the age of 20 they are considered rare in children as pointed out by Bigler and Hoyne.[1] The proportion of females to males was 3 to 2 as reported by most authors.

Ganglioneuromas originate from the sympathetic chain, or rather from the cells of the anlage of the sympathetic chain, and consequently are found in the cervical region, posterior mediastinum, posterior wall of the abdomen, posterior aspect of the pelvis and the adrenal medulla. According to Wohl[23] these tumors can also arise from elements within the central nervous system.

The posterior mediastinum is the location of almost all neurogenic tumors within the chest. Chart I shows the most likely location of most of the tumors in the mediastinum.

When a ganglioneuroma is found within the chest it is usually single, arising in the posterior gutter, extending antero-laterally, pushing the mediastinal pleura in front of it as it increases in size. This tumor does not invade lung tissue but may produce a marked atelectasis of the adjacent lung when it attains a large size. The tumor may be found protruding into a vertebral foramen forming a "dumb-bell" or "hour-glass" tumor, the retro-dural portion often enlarging to such a size as to cause cord pressure

symptoms.[5-7,19,20] This is less apt to happen with a ganglioneuroma than with a neurofibroma.[5] Heuer[7] reported 64 cases of "hour-glass" tumors of which 36 were neurogenic in origin, and five of these were intrathoracic ganglioneuromas. This author mentions four theories for the formation of the hour-glass tumors: 1) The origin of the tumor is within the spinal canal and grows outward through the intervertebral foramen. 2) The tumor arises outside of the canal and grows into the intervertebral foramen. 3) The site of origin is in the intervertebral foramen and growth takes place both inward and outward. 4) Coenen's theory is that the neurogenic tissue is present as a tumor before development of the spine and the vertebra impinges on the tumor, constricting it and giving it an hour-glass shape.

Bigler and Hoyne[1] classify tumors of the sympathetic nervous system into three basic types. These are the neuroblastomas, derived from neuroblasts, chromaffinomas or paraganglioneuromas originating from pheochromoblasts and the ganglioneuromas developing from the adult ganglion cells. Intermediate or mixed types can occur and these are congenital, originating from cell rests. The neuroblastoma is malignant and most commonly is found in children. The rare chromaffinoma is found in the suprarenal gland, carotid body, coccygeal gland and Zuckerkandl's organ. The latter tumor is usually benign although Karsner[2] states that 15 per cent are malignant. Ganglioneuromas are usually benign and when malignancy does occur, it is almost always in a mixed tumor containing areas of malignant neuroblastoma derived from undifferentiated nerve cells.[19]

Ganglioneuroma is a neoplasm in which the neurocytic element is represented by the mature or nearly mature stage of histogenesis.[17] Chart 2 bears out this statement.

The anlage of the sympathetic nervous system appears early

CHART 1

Site of predilection of tumors of the mediastinum. Taken from Gray, Shepard and Dockerty[6] and Kornblum and Bradshaw.[12]

Anterior	Middle	Posterior
Dermoid	Bronchogenic carcinoma	Lymphosarcoma
Thymoma	Lymphosarcoma	Aneurysm
Thyroid	Lipoma	Lipoma
Cysts	Aneurysm (rare)	Metastatic carcinoma
Aneurysm		Neurofibroma
Lipoma		Neuroblastoma
Metastatic carcinoma		

in the embryo and is represented by certain cells of the neural crest. Kuntz claims the sympathetic primordium consists of cells which migrate outward from the neural crests. These cells are sympathogonia. They develop into slightly larger cells with more vesicular nuclei—the sympathoblast. These are pluripotential and according to Bailey give rise to: a) neuroblasts, from which the ganglion cells of the sympathetic nervous system develop; b) pheochromocytes of the adrenal system and c) astroblasts, the glial cells of the sympathetic system which ripen into astrocytes.[10]

According to Stout[20] the ganglion cells multiply amitotically. The ganglioneuroma is composed of adult sympathetic ganglion cells and an enormous number of neurofibrils, usually without myelin sheaths. There are many Schwann cells and connective tissue cells. The numerous nerve fibrils are usually unsheathed axones and the small number of ganglion cells is due to the degeneration of earlier ganglion cells leaving the neurofibrils. However, it is possible that Schwann cells form the fibrils or that existing fibrils may split longitudinally, forming an abundance of this element in the tumor.

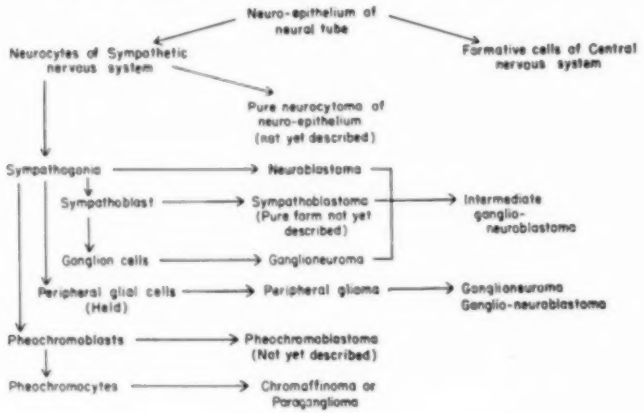
Stout[19] classified ganglioneuromas into three groups:

"I. Fully differentiated, composed entirely of adult ganglion cells with or without satellites set singly or in groups in a bulky matrix composed of enormous numbers of neurites with Schwann-

CHART 2

Prepared by Landau, modified by Schultz and taken from Bigler and Hoyne.

DERIVATION OF THE SYMPATHETIC NERVOUS SYSTEM



ian sheaths which occasionally may be myelinated, and an inconspicuous fibrous supporting framework.

"II. Ganglioneuromas with diffusely scattered cells of a lesser degree of differentiation among the completely differentiated ganglion cells. These show all degrees of variation from sympathicoblasts through sympathogonia, arranged in rosettes and pseudorosettes, and up to almost mature small ganglion cells.

"III. Composite tumors made up of two or more parts at least one of which will be fully differentiated ganglioneuroma while one or more of the other parts will be neuroblastomas."

The author states that the ganglioneuroma with sympathicoblastomatous nodules would probably be grouped with the neuroblastomas rather than with the benign group of ganglioneuromas.

In group I as much of the tumor as possible should be removed to prevent extension through an intervertebral foramen. In groups II and III they should be excised completely because of the danger of malignancy. Chart 3 shows an analysis of 199 of Stouts collection.

Symptoms

A ganglioneuroma manifests itself in many ways. No symptom complex or syndrome can be described which is diagnostic of a ganglioneuroma. The only symptoms produced by this tumor are those of pressure on adjacent nerves, bronchi and arteries. The evidence of pressure on bone is found only by x-ray studies and in the case of this particular neoplasm bone erosion is often absent. Gray, Shepard and Dockerty[6] have compiled a list of symptoms produced by this tumor and much of our discussion on symptoms is taken from them.

Pressure on the recurrent laryngeal nerve may produce a change in voice quality with a brassy cough. If the destruction of this nerve is complete, stridor may result from paralysis of the cricoarytenoid muscle. Pressure on a bronchus may produce a dry, nonproductive cough and even result in decreased aeration causing dyspnea, orthopnea and cyanosis. If the occlusion of the bronchus is complete, atelectasis occurs. A sensation of fullness

CHART 3

An analysis of neurogenic tumors, including ganglioneuromas, taken from Stout.

Group	No.	Classification	Metastasis
I	146	Differentiated	No
II	33	Partially differentiated	6
III	20	Undifferentiated	13

in the chest has been described and occasionally dysphagia has been one of the complaints. Edema of the upper half of the body has been reported as well as facial cyanosis with dilatation of veins in the face and neck from pressure on the superior vena cava.

Horner's syndrome is frequently present after surgery, as reported by Stout,[20] Heuer and Andrus[8] and Gray, Shepard and Dockerty,[6] which is due to injury or section of the cervical sympathetic chain. An interesting occurrence is reported by Stout[20] in the fact that a dilated pupil on the operated side followed removal of a cervical ganglioneuroma. The pupil remained dilated for a period of two to three years and then returned to normal. There seems to be no doubt of this dilatation since the patient was under the observation of a physician during this entire time. Stout offers an explanation of this by quoting Weibrand and Sanger's textbook[22] which describes Langendorf as having found a paradoxical dilatation of the pupil on the same side after experimental extirpation of the superior cervical ganglion. The occurrence postoperatively of a Horner's syndrome has been reported frequently in cervical as well as intrathoracic ganglioneuromas especially when the latter are located high in the thorax.[6] Pancoast[14] in 1924 described the pre-operative occurrence of Horner's syndrome associated with pain on the inner surface of the arm, third, fourth and fifth fingers, loss of touch, weak wrist extension and loss of grip in the hand. He associated this with a tumor in the apex of the chest. In 1932[15] he restated his syndrome, setting forth five requirements that must be met for a tumor to conform to it.

1) Location of tumor in thoracic inlet in the region of the superior pulmonary sulcus.
2) Pain around the shoulder and down arm.
3) Atrophy of muscles of hand.
4) Horner's syndrome (essential for diagnosis).
5) X-ray evidence of a small homogeneous shadow at the extreme apex with local destruction of ribs and infiltration of vertebrae.

The author stated that a primary tumor of lung, pleura, ribs or mediastinum could be excluded by the absence of one or more of the foregoing characteristic manifestations. This does not always hold true, as shown in our following report. The production of Horner's syndrome is dependent on pressure exerted by the tumor on the cervical sympathetic chain, and frequently on the stellate ganglion. If pressure on the first thoracic sympathetic ganglion is minimal or absent, no Horner's syndrome will result, even though a superior sulcus tumor exists.

Symptoms of cord pressure may result if the tumor protrudes

into an intervertebral foramen assuming a dumb-bell shape. Hart and Ellison have described a Pel-Epstein type of fever in mediastinal ganglioneuroma although this has not been found in individual reports. A cervical mass may be associated with a mediastinal tumor. In this case the origin is usually from the cervical sympathetic chain.

X-ray study reveals a well-circumscribed mass, usually in the posterior mediastinum, and may not show evidence of bone erosion of a rib or vertebral body. It is evident that the symptoms depend on the size and location of the tumor rather than any particular symptom derived from the tumor tissue itself. There is no evidence of hormonal disturbance.[19] The differential diagnosis is summarized in Chart 4.

The exact diagnosis of a ganglioneuroma cannot always be made pre-operatively. A presumptive diagnosis may be made in the light of x-ray findings of a large, oval, smooth, mediastinal tumor, present for years without symptoms, without evidence of metastasis, in a person under 25 and in good physical condition. These tumors are usually benign, although Saphian[18] has reported the occurrence of malignant changes.

Surgery is indicated in all mediastinal tumors, because of their potential malignancy. The tumor is most likely malignant if the x-ray shadow is not clearly defined, if its size shrinks demonstrably after x-ray therapy, or if there are signs of metastasis. Thoracotomy should be avoided unless further study after artificial pneumothorax should indicate that the lesion might be benign. Death is caused by growth in size, malignancy or infection. The complications of surgery include hemorrhage, infection and meningitis.[6] The most serious of these is the hemorrhage, which is often sudden and profuse because of the close association of these tumors with the major vessels of the mediastinum. The blood supply to the tumor is often directly from the aorta.

CASE REPORT

Mrs. J. D., a 26 year old colored female was admitted to the hospital on September 23, 1948 with the complaint of pain in the left arm and shoulder for 1½ months. The pain centered in the posterior portion of the shoulder and radiated into the medial aspect of the arm and forearm to the little and ring fingers. It was present constantly, was not aggravated by exercise and was not accompanied by dyspnea or cyanosis. There was no history of trauma. Weight had remained constant. She had no previous surgery and only the usual childhood diseases.

Physical examination revealed a B.P. 120/75, pulse 88, temperature 98.0 degrees F., and she was well developed and nourished. Head and neck were negative, pupils were equal and reacted to light. The heart was normal. The chest revealed a marked decrease in tactile fremitus and dullness on percussion over the left upper lobe both anteriorly and

CHART 4

Tumor	Location in Mediastinum	Growth	Metastasis	Response to X-ray	Contour	Remarks
Ganglioneuroma	Posterior	Slow	No	No	Smooth	
Intrathoracic thyroid	Lateral	Slow	No	No	Smooth	Deviated trachea, palpable
Cyst	Anterior	Slow	No	No	Smooth	Rarely post. to trachea
Teratomas	Anterior	Slow	Yes	No	Smooth	Calcification
Lymphoblastoma (Hodgkin's)	Anterior, Middle or Posterior	Rapid	Adenopathy	Yes Slowly	Nodular	Biopsy node
Neurofibroma	Posterior	Slow	No	No	Smooth	
Lipoma	Anterior, Middle or Posterior	Slow	No	No	Smooth	
Leukemia	Anterior, Middle or Posterior	Rapid	Adenopathy	Yes	Nodular	WBC
Aneurysm	Anterior or Posterior	Slow	No	No	Smooth	Fluoroscopy
Metastatic Carcinoma	Anterior, Middle or Posterior	Rapid	Primary tumor	Yes	Nodular	Primary tumor
Enlarged Thymus	Anterior	Rapid	No	Yes	Irregular	

posteriorly. There was no resonance over Kronig's isthmus on the left. The left supraclavicular fossa was more full than the right, but no mass could be palpated. There was no adenopathy in the neck or axilla. The abdomen was normal. The reflexes were physiological and there was no muscle atrophy.

Laboratory findings: RBC, 3,910; Hemoglobin, 11 Gm. (71 per cent); Color index, 1; WBC, 7,500; differential count: Lymphocytes, 23 per cent; Polymorphonuclears, 75 per cent and Monocytes, 2 per cent. The urine

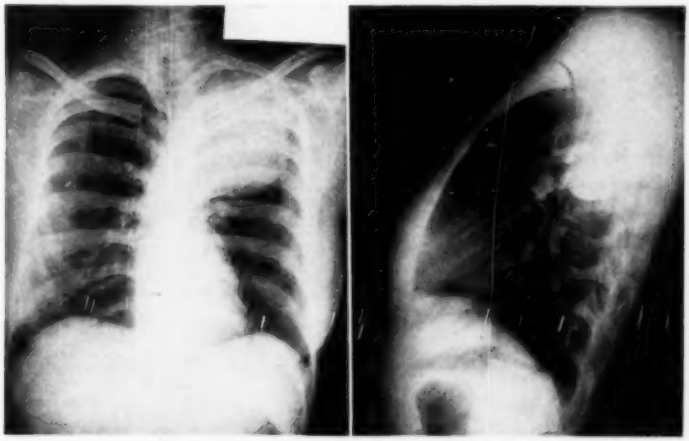


FIGURE 1a FIGURE 1b

Fig. 1a: X-ray film shows a large, well defined tumor of the upper left pleural cavity.—*Fig. 1b:* Left-lateral view locates tumor in the posterior portion of the chest.

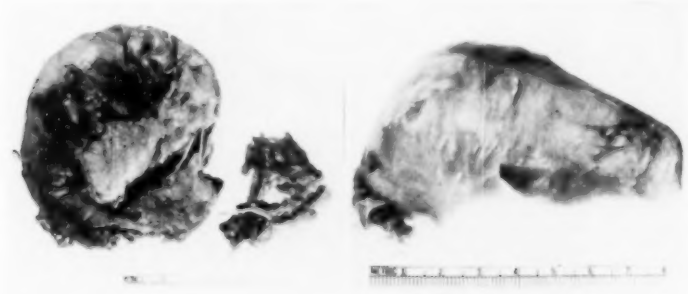


FIGURE 2a FIGURE 2b

Fig. 2a: The gross specimen is on the left. The small structure on the right is a portion of the thoracic sympathetic chain composed of the ganglions T-2, T-3 and T-4.—*Fig. 2b:* The cut surface of the tumor. A small portion of the thoracic sympathetic chain is seen on the left.

showed a specific gravity of 1.014, no albumin or sugar, and microscopically there were 12 to 15 white blood cells per high power field. Blood Kahn test was negative.

X-ray revealed a large tumor mass in the upper posterior portion of the thorax (Fig. 1). The preoperative diagnosis was neurofibroma or ganglioneuroma.

On the 2nd of October left thoracotomy was performed by posterior approach through the 5th intercostal space. Exposure was facilitated by fracturing the 5th and 6th ribs and separating the incision with rib spreaders. The tumor mass was seen to originate from the thoracic autonomic ganglions T_1, T_2, T_3 and T_4 with apparent extension into the second thoracic intervertebral foramen. The blood supply of the tumor was apparently derived directly from the aorta by several small arteries. The tumor was removed, hemostasis established, and the chest was closed, with two mushroom catheters in the pleural space for expansion of the lung and drainage.

The operative diagnosis was a ganglioneuroma (Fig. 2) and the microscopic sections substantiated this diagnosis (Fig. 3).

Horner's syndrome was present on the left immediately after the operation. On the sixth day, after x-ray inspection of the chest showed complete expansion of the lung, the catheters were removed. The postoperative course was uneventful and the patient left the hospital on the

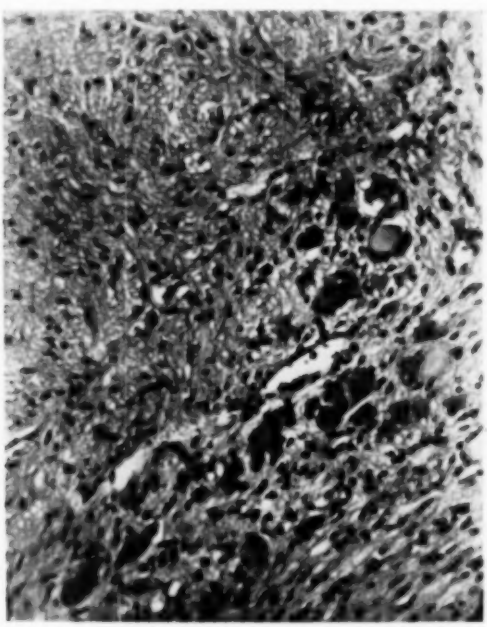


FIGURE 3: Photomicrograph of specimen showing adult ganglion cells surrounded by neurofibrils and fibrous tissue. (Hematoxylin and eosin, X 220).

10th postoperative day. One month later the Horner's syndrome had disappeared and both pupils were equal.

By that time, an x-ray inspection of the chest (Fig. 4) showed complete reexpansion of lung. The tumor shadow was gone, and the silver clip shown in Figure 4 is at the lower aspect of the tumor pedicle.

SUMMARY

1) An attempt has been made to review the literature to date concerning intrathoracic ganglioneuroma.

2) A case is reported with successful removal of the tumor.

3) A search of the literature has been made to bring the number of intrathoracic ganglioneuromas reported to date, since the collection of Heuer and Andrus in 1940. These are listed in chronological order after the references. Twenty-one were found and these added to the 68 reported by Heuer and Andrus, including our own, brings the total to 90.

RESUMEN

1) Se ha revisado la literatura médica hasta el presente, con respecto a los ganglioneuromas endotorácicos.

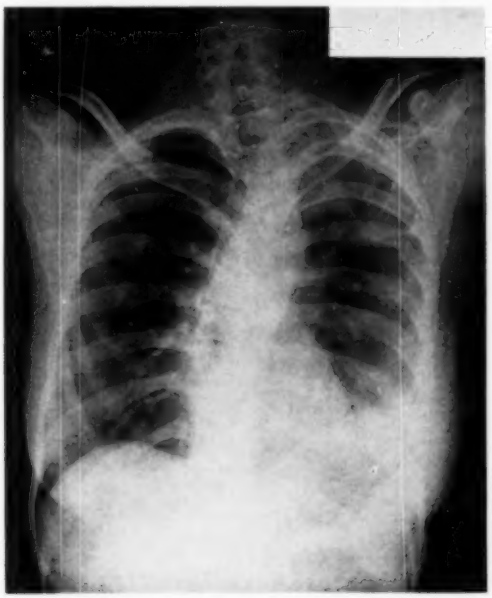


FIGURE 4: Postoperative film of chest shows absence of tumor and the surgical fractures of fifth and sixth ribs. The silver clip seen in the fourth interspace was placed just distal to the point of section of the sympathetic chain.

2) Se presenta un caso, el cual se ha extirpado con éxito.

3) Se ha investigado la literatura médica hasta el presente, en todos los ganglioneuromas endotorácicos publicados, desde la colección de Heuer y Andrus en 1940. Estos se han enumerado en forma cronológica después de la bibliografía. Los veinte y un casos nuevos, fueron agregados a los 68 casos de Heuer y Andrus, incluyendo el nuestro, formando un total de 90 casos.

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Sarcoidosis and Pregnancy*

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Since May 1948, x-rays of the chest, utilizing 70 mm. photofluorographic equipment, have been taken routinely of all patients admitted to the wards of the Morrisania City Hospital, except those in critical condition. Of 10,000 x-ray films taken in the past year, approximately 85 per cent of the total admissions, 1287 were of women registered in the prenatal clinic who were subsequently delivered at the hospital. Among the 1287 prenatal x-ray films of the chest, three instances were discovered presenting roentgenographic findings suggestive of sarcoidosis. In two, the diagnosis was confirmed by biopsy.

Inasmuch as sarcoidosis is occasionally discovered in young women of the child-bearing age, and since this disease is suspected by some of being an atypical form of tuberculosis, the occurrence of sarcoidosis and pregnancy in the same individual has a practical bearing. One is faced with the problem of the safety of the expectant mother and what effect, if any, the disease may have on the newborn. The pregnancy in each of our patients was allowed to go to term.

A review of the literature of the past 10 years fails to disclose a single instance of intrathoracic sarcoidosis associated with pregnancy. A case was reported by Nordland, Ylvisaker, Larson and Reiff,[1] of a 26 year old white housewife with thrombocytopenic purpura. Splenectomy was successfully performed in the fifth month of pregnancy. Examination of the extirpated spleen showed sarcoidosis. The pregnancy terminated normally at term.

Case Reports

Case 1: R.B., a colored housewife, aged 21 years, grava three, para two, registered at the Morrisania City Hospital, Prenatal Clinic, in the second month of pregnancy. A routine prenatal x-ray inspection of the chest on August 3, 1948, in the third month of her pregnancy, revealed bilateral hilar lymph node enlargement (Fig. 1A). The patient was asked to return for further study but by the time she appeared, two months later, she had developed painless swellings of the parotid and lacrimal glands.

On admission to the hospital, the physical examination disclosed a well nourished female in no obvious discomfort. Both parotid glands were swollen, the left larger than the right (Fig. 1B). The lacrimal glands

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were enlarged but not tender. There was no palpable adenopathy anywhere else in the body. The breasts were soft and contained no masses. The lungs were clear to percussion and auscultation. The heart revealed nothing abnormal. The liver and spleen could not be felt. The skin over the extensor surface of both legs was studded with lichenoid papules, pinkish in color. Neurological examination showed a mild right facial weakness and left trigeminal hypalgesia.

Repeated x-ray films of the chest revealed the same degree of enlargement of the hilar lymph nodes as noted in the initial film. Roentgenograms of the hands and feet, sella turcica and Stenson's duct revealed no abnormalities. Numerous examinations of the sputum failed to reveal acid-fast organisms. The patient did not react to tuberculin in concentrations up to 1 mg. intracutaneously. The results of some of the other laboratory examinations were as follows: Electrocardiogram of the heart was within normal limits. Mazzini was negative. The urinalysis was normal. The white blood cell count was 4,900 per cubic millimeter, with 64 per cent polymorphonuclear cells, 32 per cent lymphocytes and 4 per cent monocytes. The red blood cell count was 3,720,000 and hemoglobin was 11 gm. Erythrocyte sedimentation rate was 18 millimeters in 30 minutes. Total protein was 5.2 gm.; albumin, 4.1; globulin, 1.1. Calcium, 9.6 mg.; phosphorous, 2.5 mg. and alkaline phosphatase, 4.1 KA units. Uric acid was 2.3 mg. and urea nitrogen was 7 mg. per 100 cubic centimeters. Cholesterol was 363 mg. per 100 cubic centimeters and esters 168.

An aspiration biopsy of the right parotid gland showed round cell infiltration on microscopic examination. A skin biopsy of one of the papules showed some areas in the corium suggestive of epithelioid

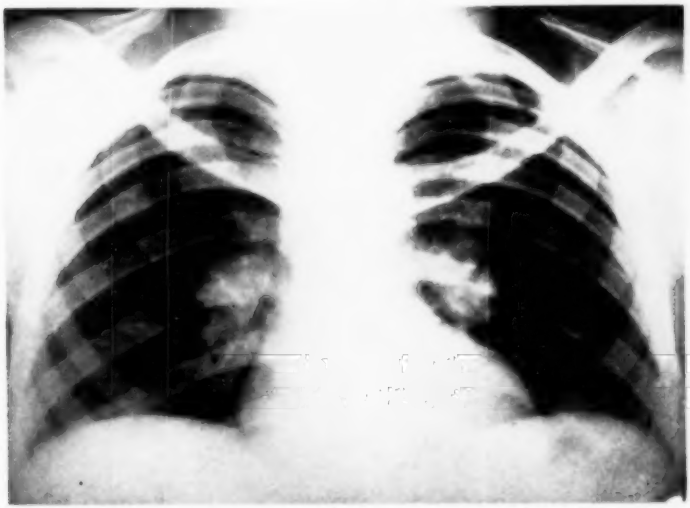

FIGURE 1A: Case R.B. Prominent hilar lymph nodes. Slight upward displacement of both leaves of the diaphragm. Discovered in course of a routine prenatal examination of the chest.

tubercles, but these were not sufficiently characteristic to make a precise diagnosis.

The patient remained afebrile and asymptomatic. After a stay of five weeks at the hospital, she was discharged and followed in the chest and prenatal clinics. By January 1949, the swelling of the parotid glands had decreased considerably but the condition of the lacrimal glands remained unchanged.

On February 5, 1949, the patient was admitted to the hospital in active labor. A transverse presentation was encountered. The fetal heart was good but disappeared as labor progressed. A version and extraction of a stillborn male child was done. Necropsy of the fetus revealed atelectasis of both lungs, cerebral edema and minute cerebral hemorrhages. The diagnosis was asphyxiation. There was no evidence of sarcoidosis or tuberculosis. The mother's postpartum course was uneventful.

In March 1949, the patient returned to the Chest Clinic complaining of pain in the left breast. Examination revealed a plum-sized mass in the left upper quadrant. Biopsy of this mass showed hyperplastic breast acini and ducts, with many small tubercles consisting of epithelioid cells, connective tissue and giant cells but no caseation. The diagnosis was sarcoidosis. Follow-up examinations have shown no significant changes in the x-ray findings. The swelling of the parotid glands has subsided completely but the right lacrimal gland enlargement is still present.

FIGURE 1B: Two months later, development of parotid swellings and enlarged lacrimal glands (Mikulicz's syndrome).

Recapitulation: A colored woman of 21 was found to have enlarged hilar lymph nodes in the course of a routine prenatal roentgen-ray inspection of the chest. Shortly thereafter she developed painless swellings of the parotid and lacrimal glands (Mikulicz's syndrome). Biopsy of a nodule above the left breast revealed tissue consistent with a diagnosis of sarcoidosis. The pregnancy was allowed to go to term and the patient delivered a stillborn child. The patient has remained well.

Case 2: A.C., a colored housewife, aged 23 years, grava two, para one, had a normal delivery at the Morrisania City Hospital in February 1947. Shortly thereafter she developed weakness and fatigue. On July 23, 1948, she was examined at the prenatal clinic and was found to be pregnant. Because of a nonproductive cough of one month's duration she was referred to the chest clinic and then to the ward.

Physical examination revealed a well developed female in no distress. The chest was clear to percussion and auscultation. The breasts were normal. The liver and spleen were not palpable. A roentgenogram of the

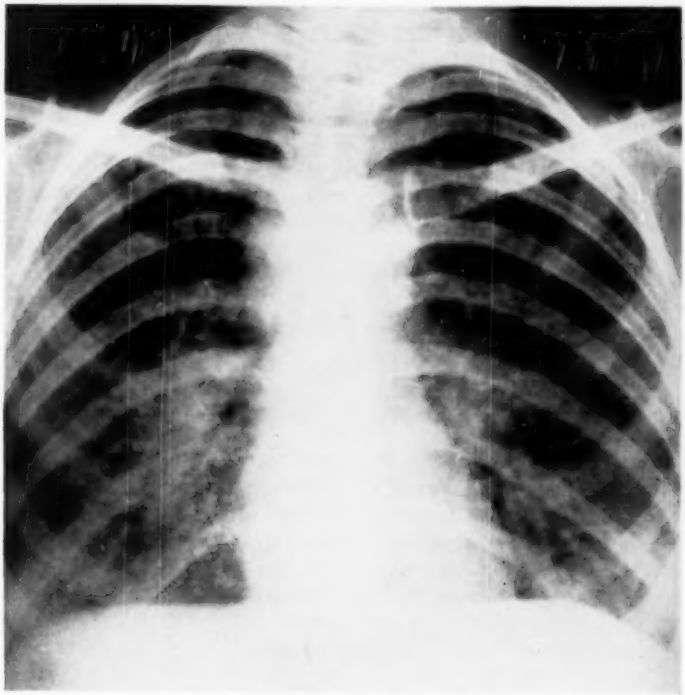

FIGURE 2: Case A.C. Miliary and nodular infiltrations diffusely involving both lungs, especially the bases.

chest showed disseminated miliary and nodular infiltrations in both lungs, more pronounced in the lower lobes (Fig. 2). In view of the recent history of pregnancy, as well as age and color of the patient, tuberculosis was suspected. However, the paucity of the symptoms was also in keeping with sarcoidosis. A palpable lymph node was found in the left epitrochlear region. The node was excised and histologic examination showed many epithelioid tubercles containing occasional giant cells resembling Langhans cells with a surrounding zone of lymphocytes. There was no caseation. The diagnosis was sarcoidosis.

Repeated examinations of the sputum failed to reveal acid-fast bacilli. The patient failed to react to tuberculin in concentrations up to 1 mg. Roentgen-ray inspection of the hands and feet showed no abnormalities. Other laboratory tests were negative. The urine was normal. Mazzini was negative. Total protein was 6.6 gm., albumin, 4.3 gm. and globulin was 2.3 gm.

The patient was asymptomatic and afebrile, except for occasional dry cough. After a month's observation in the hospital, she was discharged to the chest and prenatal clinics, where she was followed until she went into labor, April 5, 1949. She was readmitted and delivered a normal male child in six hours. The postpartum course was uneventful. The mother and baby were discharged in good condition on the sixth postpartum day. The patient is now attending the chest clinic. Roentgenograms of the chest have shown no change.

Recapitulation: A colored woman of 23 years developed weakness, fatigue and dry cough following delivery of a healthy child 18 months previously. She again became pregnant. A roentgenogram of the chest revealed miliary and nodular infiltrations in both lungs simulating hematogenous tuberculosis. Repeated sputum examinations failed to reveal acid-fast organisms. Biopsy of an epitrochlear lymph node revealed sarcoidosis. The pregnancy was allowed to go to term and the patient delivered a healthy child. The patient has remained well.

SUMMARY

Two instances are reported of colored women, aged 21 and 23 years respectively, who became pregnant and in whom sarcoidosis was discovered. The diagnosis of sarcoidosis was proved by biopsy of breast tissue in one instance and of an epitrochlear lymph node in the other. The pregnancies were allowed to go to term. One patient gave birth to a stillborn; the other to a healthy infant. The pregnancies did not affect the course of sarcoidosis nor did the sarcoidosis influence the pregnancies. Although no conclusions can be drawn on the basis of such a small series of cases, there is reason to believe that pregnancy and sarcoidosis may coexist without affecting each other.

RESUMEN

Se refieren dos casos de mujeres de color de 21 y 23 años estando embarazadas en quienes se descubrió que padecían sarcoidosis.

El diagnóstico se comprobó por biopsia de tejido de la mama en un caso y de un ganglio epitrocleano en el otro.

Los embarazos fueron dejados llegar a término. Una de las enfermas dió a luz un producto muerto; la otra un niño sano.

Sarcoidosis y embarazo no se influenciaron reciprocamente.

Aunque no se pueden extraer conclusiones de tan pocos casos hay razón para creer que la sarcoidosis y el embarazo pueden coexistir sin afectar una a otro.

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The Pathogenesis of Tuberculosis

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Introduction

There are many unanswered questions concerning the pathogenesis of tuberculosis. However, this complex subject is made more complicated by lack of uniform terminology, failure to recognize many events that may occur regardless of any difference of opinion in regard to their origin, failure to recognize fully the factors modifying the development of tuberculous disease under different conditions and in different localities, and lack of adequate control observations.

Some Basic Terms

Recognition of the terms to be employed is paramount in any discussion. A *primary focus* is the lesion produced in any tissue where the first infection with tubercle bacilli occurs. The *primary complex* includes the primary focus and the involved efferent lymphatic vessels and nodes. A *progressive primary lesion* is one which results from direct or contiguous extension of disease from a primary focus, with or without a period of comparative inactivity. *Endogenous exacerbation* refers to a reactivation of a disease locus that has remained dormant for a variable period of time. *Exogenous reinfection* indicates a new infection from without which occurs in an individual who has a healed tuberculous infection. *Superinfection* (if it exists) consists of infection from an external source which is superimposed upon an unhealed tuberculous lesion. *Miliary tuberculosis* refers to numerous "millet-sized" lesions uniformly distributed through an organ or throughout the body, and implies a hematogenous dissemination of infection. A *tuberculoma* is an isolated lesion of variable size which contains a caseous center and tends to be encapsulated. This lesion may be entirely replaced by fibrous tissue. It is seen in the liver or brain as a result of hematogenous dissemination, but in the lung it may result from bronchogenic spread (round foci). *Miliary endobronchial metastases* are small lesions initiated by secondary extension through the bronchi, and lack the homogenous distribution of a hematogenous spread. *Phthisis* indicates a "wasting" or progres-

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sive disease, more or less limited to an organ system, and is usually used in connection with lung disease.

Portals of Entry[1-3]

In countries where pasteurization of milk is extensively practiced the portal of entry is via the respiratory tract in well over 90 per cent of the cases. Occasionally there is infection via the oral cavity with a primary focus in the tonsil or in the gastrointestinal tract. The skin has been mentioned as a portal of entry in ritual circumcision and rarely at other sites of trauma. Transmission through the placenta is rare, but is reported. One portal of entry, for example the tonsil, may not preclude a later portal of entry in another tissue such as the lung.

Modes of Spread[2]

Tuberculous infection may be propagated by contiguous spread, via lymphatics or blood stream, by lymph-hematogenous spread (e.g., thoracic duct to left subclavian vein), through the bronchial tree (bronchogenic spread), or by intracanalicular spread (e.g., bronchi to trachea to larynx to gastro intestinal tract).

Basic Pattern of Tuberculous Infection

The individual is unaware of the entrance of tubercle bacilli into the body for some time. The primary focus of infection in the lungs may be located in any lobe, usually subpleurally. After an incubation period of three to eight weeks (average four to six weeks), the tuberculin reaction can be elicited and the primary focus or primary complex may or may not be visible upon x-ray examination. Levine[4] found 16 children who had lesions demonstrable by roentgenogram before the development of tuberculin reaction. However, in most cases the reverse may be true. Usually the roentgen signs, when present, may be demonstrated within 10 to 16 weeks after infection occurs. Indeed, the tuberculin reaction may be the only indication of infection, or the period of initial invasion may be accompanied by symptoms and signs. These include fever, malaise, anorexia, weight loss, cough, wheezing, increased erythrocyte sedimentation rate, neutrophilic leukocytosis followed by monocytosis or lymphocytosis, phlyctenular conjunctivitis and erythema nodosum. The last-mentioned is quite common in the Scandinavian countries, but is uncommon in the United States. The subsequent course of events may be modified by factors of individual resistance, age, sex, race, socio-economic factors, etc.[2] The period of initial invasion is especially dangerous in the ages of birth to three years and from 15 to 35 years, which Wallgren designates as the first and second danger periods.[1] It is like-

wise dangerous in the Negro and in some social groups, and seems to be influenced by geographic variations (e.g., less dangerous in Minnesota than in the Scandinavian countries).

During the stage of initial invasion there is usually a "first hematogenous spread." By this is meant that in most cases tubercle bacilli are disseminated throughout the body by the blood stream, probably before[6] the tuberculin reaction is in evidence. Subsequent lesions tend to be localized by the Koch phenomenon when allergy develops. However, generalized hematogenous miliary tuberculosis or meningitis may result at this time, or the foci may tend to heal only to reactivate at a later date.

After four to six months (but sometimes longer) the initial complex tends to stabilize, and to heal by fibrosis, calcification and/or resolution.[7] The patient may thus have completed the triad depicted in figure 1, and yet fully 75 per cent may not show evidence of disease on the roentgenogram. On the other hand, the primary lesion may proceed directly or after a variable latent period to a more advanced disease process,[8] or even to a wasting phthisis,[9] with extensive involvement of the contiguous pulmonary tissue (figure 2). Also, a non-caseating or serous pneumonia may develop in the surrounding area, and bronchial compression or invasion may lead to obstructive emphysema,[10] including formation of cyst-like blebs or bullae, and atelectasis. These latter conditions were previously designated as "epituberculosis" to designate that the entire roentgenographic picture did not consist of caseous or tuberculous inflammatory tissue, and could resolve in a few months, leaving at times only a small fibrous or calcific nodule as evidence of disease. This atelectasis may result in bronchiectasis in a high percentage of cases, however, if it doesn't resolve within 9 to 12 months.[11]

Since the primary lesion is usually located subpleurally, only

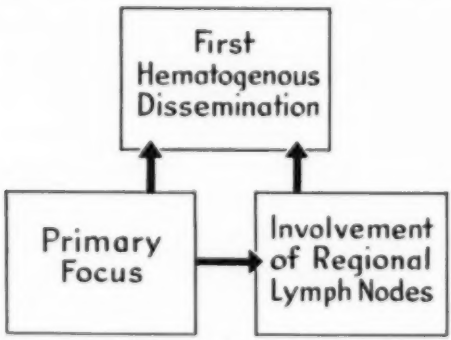

FIGURE 1: Basic Pattern of Infection.

minimal extension is required to reach the pleural surface, and pneumothorax or pleural effusion may result.

If the primary lesion appears to be controlled, an endogenous exacerbation or exogenous reinfection may lead to bronchogenic dissemination of disease. This quite commonly results in the subclavicular minimal infiltrate, single or multiple tuberculomata (round foci) or miliary endobronchial metastases. Apico-caudad extension may then produce moderately advanced or even far advanced lesions. At any time during this progression the bacilli may enter the blood stream for a secondary hematogenous dissemination, or a small focus of disease in some other organ may reactivate, progress and invade the blood stream.

Superinfection, occurring in the presence of unhealed lesions, may be a factor, but this still awaits definite proof. It is included only for completeness.

Thus, phthisis or wasting of the lung tissue may result from the progression of the primary lesion, endogenous exacerbation, exogenous reinfection, or from any one of the three plus the possible superinfection, if the balance of bacillary virulence and host resistance is disturbed. This progressive disease may occur in organs or systems other than the lungs. At any stage of disease in any organ a lesion may progress to produce local phthisis or to invade the blood stream.

What Happens to Involved Regional Nodes? (figure 3)

We have already discussed the various consequences of the primary focus. The nodal lesions may likewise heal or proceed to

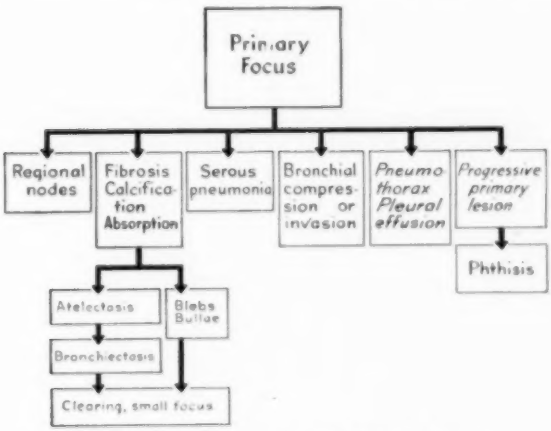

FIGURE 2: What Happens to the Primary Focus?

caseation. The caseous node may perforate a bronchus,[12] leading to positive sputum, and the bacilli may take the intracanalicular route to the larynx and gastro-intestinal tract. Bronchial compression or invasion leads to manifestations of obstructive emphysema or atelectasis. Discharge of a large caseous mass may result in a complete blockage of the rima glottis with sudden death. The caseous node may perforate the thoracic duct and the bacilli are then conducted to the subclavian vein to initiate a hematogenous dissemination. Rupture of caseous material into the pericardium may cause tuberculous pericarditis. Calcified hilar nodes may produce bronchostenosis,[13] leading to future difficulties such as recurrent pneumonias and atelectasis, which may in turn lead to bronchiectasis.

What Happens to the Progressive Primary Lesion?

In figure 4 the progressive primary lesion and its subsequent possibilities are shown. Briefly, it may heal, spread through the surrounding tissue, involve the bronchial tree, or invade the blood stream.

What Happens to the First Hematogenous Spread? (figure 5)

A transient bacilluria may be the only demonstrable evidence of the first hematogenous spread. This may occur in the absence of any other urinary findings, and some even believe that the tubercle bacilli go through the intact glomerulus. This is difficult to prove. Hematogenous miliary tuberculosis or meningitis may

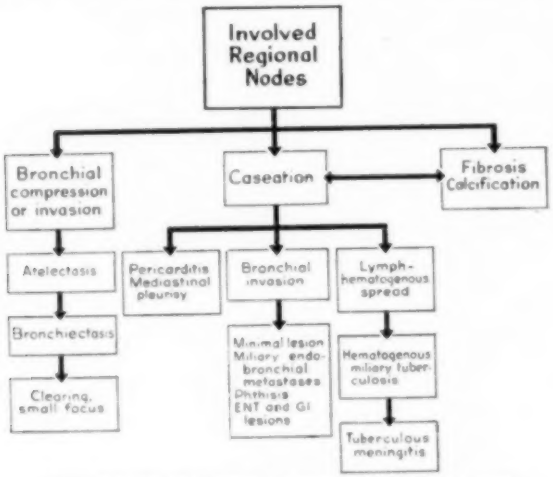

FIGURE 3: What Happens to Involved Regional Nodes?

occur. More often the disseminated foci remain quiescent, but may reactivate after a period of a few months or years, giving rise to progressive organ disease and at times to a secondary hematogenous spread. Thus, a chest roentgenogram may reveal an active lesion, an apparently healed lesion, or nothing at all, while a progressive tuberculous lesion is present in the skeletal system or kidney.

Bone tuberculosis frequently starts in the metaphysis, less fre-

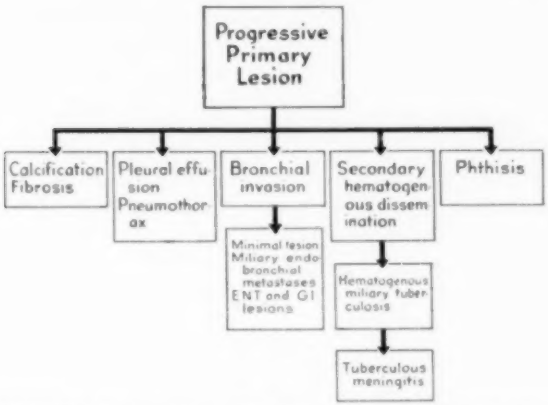

FIGURE 4: Consequences of First Hematogenous Dissemination.

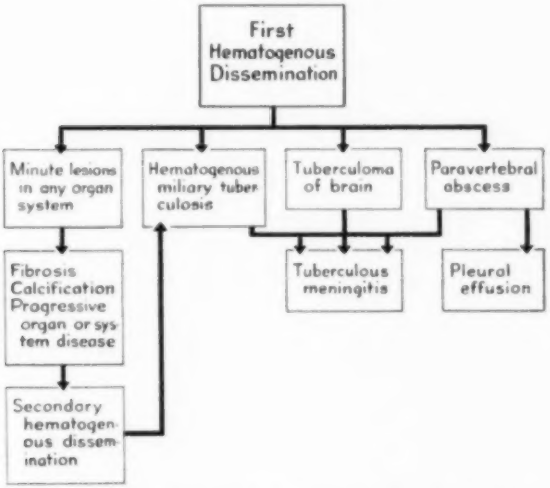

FIGURE 5: What Happens to Progressive Primary Lesions?

quently in the epiphysis. The lesions may penetrate the joints, slowly destroying the cartilage.[14] Poncet's rheumatism is an "allergic" type of joint swelling which may disappear in two to three weeks, and does not indicate the presence of tubercle bacilli in the joint space. Rarely, cyst-like lesions appear in the diaphyses of the long bones and the phalanges (spina ventosa), simulating lesions seen in sarcoid and coccidoidomycosis. Tuberculosis of the spine is the most frequent type of bone tuberculosis; this may lead to the formation of paravertebral abscess, and thus be responsible for the development of meningitis or pleural effusion.

In the brain solitary or multiple tuberculomata may form. Large areas of involvement in the mid-brain may lead to ventricular block, and cortical lesions may rupture into the subarachnoid space[2] to produce meningitis. Meningitis may be "bacillary" (with demonstrable bacilli) or "serous" (without demonstrable bacilli).

In the liver, spleen and kidneys single or multiple foci may either heal and calcify or form progressive lesions. Renal tuberculosis[15] spreads inward from the cortex to the renal pelvis and thence by intracanalicular spread downward. Tuberculous salpingitis may spread to involve the ovaries or uterus. Lesions of the uveal tract and choroid of the eye may be noted in some cases. Involvement of the adrenals may produce Addison's disease, and the rare pancreatic tuberculosis may lead to signs of pancreatic insufficiency and skin pigmentation.

Pathogenesis of Phthisiogenic Infiltrates

From the preceding discussion and in figure 6 it is seen that a wasting phthisis may occur in any organ in which any tuberculous lesion may progress by spreading through the contiguous tissue. Thus, this possibility must be kept in mind from the time of the appearance of the primary focus until the death of the patient. This would seem to indicate that the therapy of the patient should depend upon the pathoiogical process present, and not be limited by the designation of a lesion as primary or other form of tuberculosis.

The Secondary Hematogenous Spread

The secondary hematogenous spread is a term used in this paper to indicate any hematogenous dissemination of disease that occurs after the first hematogenous spread. It may occur in patients who have a progressive primary lesion in the lung as well as in those who have lesions that have spread to other parts of the lungs. It may be initiated in an area of infection that has been previously established by the first hematogenous dissemination. At postmortem one may find a hematogenous miliary tuberculosis or

tuberculous meningitis and after thorough search find only a small caseous process in bone, kidney, prostate, etc., that has produced the overwhelming infection by invading the blood stream. Any unhealed lesion in any organ may progress and invade the blood stream.

Effect of Non-Specific Diseases

In children incidental disease such as non-tuberculous pneumonia, upper respiratory infections, etc., may result in visible progression of disease. In adults, on the other hand, the sputum may temporarily turn positive, but demonstrable progression or extension of disease is less likely to occur. Necrotizing pneumonia is most potent in activating tuberculous lesions.[16] Satisfactory collapse usually prevents spread.

The presence of incidental infections may also lead to the false conclusion that tuberculous disease has progressed. Certainly in reading chest roentgenograms, the possibility of viral and non-tuberculous bacterial pneumonias, Loeffler's eosinophilic infiltration, lipiodal reactions after bronchograms and pleural effusions such as occur in disseminated lupus erythematosis must be kept in mind.

The Negative Tuberculin

Failure to react to tuberculin may signify that the individual has never sustained tuberculous infection or is in the preallergic incubation period. A small percentage of patients heal their infec-

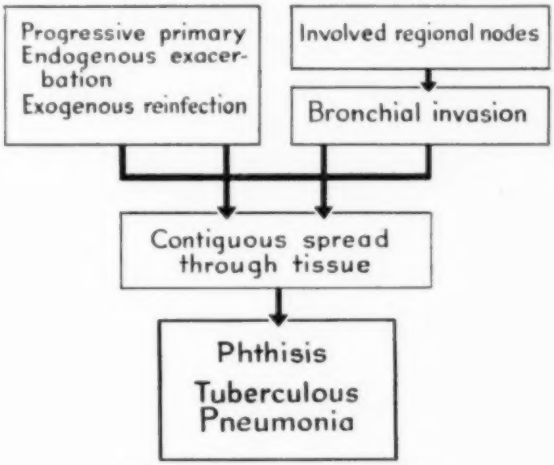

FIGURE 6: Pathogenesis of Phthisis.

tion and the allergy subsequently disappears. The tuberculin test may become negative temporarily as a result of an incidental infectious disease such as measles, in the late stages of generalized miliary tuberculosis or meningitis, or after an overwhelming seeding of the pleural space following rupture of a subpleural focus. Inadequate technique is not an uncommon factor. Some patients apparently never or only intermittently have skin allergy even in the presence of active disease.

Whether sensitivity to tuberculin without active disease protects the individual has been discussed widely for many years. This status may be attained in persons who have controlled a first infection, and the proponents of BCG vaccination state that they produce the tuberculin reaction without harm to the individual.

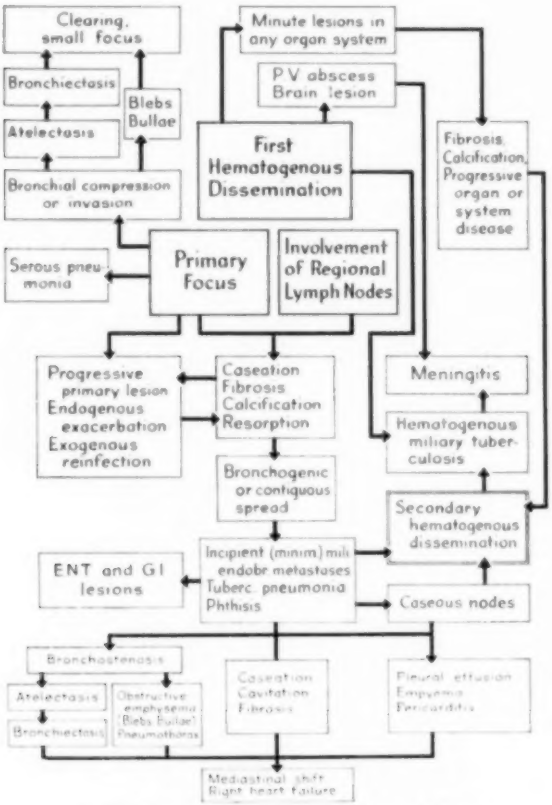

FIGURE 7: Composite Pattern of Possibilities.

Cellular transfer of tuberculin sensitivity has also been reported.[17] Although allergy and immunity appear to be due to separate factors[2] they usually co-exist to some degree. Some say that allergy is dangerous, while others claim that the protective immunity that co-exists with the allergy more than offsets this danger. Many studies discussing this problem have been inadequately controlled, but it is hoped that in a few years more scientific conclusions may be drawn. Regardless of the results, other tried and proved methods of control must not be neglected. Further discussion of this problem is beyond the scope of this paper.

Discussion

The study of tuberculosis has many interesting facets. The diagnosis alone is often difficult to establish, and Garland[18] lists 89 conditions that have caused confusion in chest roentgenograms alone. Beyond this each case poses an individual problem of management, and public health control aspects form grounds for endless discussion. Many physicians find themselves lost in the controversial opinions expressed in the literature. However, it seems logical that the adoption of uniform terminology and the recognition of a unified conception of the development of tuberculous lesions as depicted in figure 7 may form a basis of thought to aid one in the study of tuberculosis in its various aspects.

SUMMARY AND CONCLUSIONS

The basic pattern of tuberculous infection has been discussed. Various theories of the mechanisms involved have been purposely omitted in many instances, and indeed, many are unsolved. It is hoped that further research and clinical observations will serve to clarify further the evolution of this disease. Although we may not be able to state dogmatically that a given lesion is a progressive primary lesion or is the result of endogenous exacerbation or exogenous reinfection, a unified concept of the pathogenesis of tuberculosis will aid in the interpretation and management of each individual case.

RESUMEN Y CONCLUSIONES

Las formas básicas de la infección tuberculosa se discuten. Varias teorías de los mecanismos que se ponen en juego se han omitido intencionalmente y desde luego muchos mecanismos no están aclarados. Se espera que estudios ulteriores y la observación clínica servirán para aclarar la evolución de la enfermedad.

Aunque estamos incapacitados para asentar dogmaticamente si una lesión es primaria progresiva o es resultado de una infección exógena, una unificación del concepto patogénico de la tuber-

culosis ayudará para interpretación y el tratamiento de cada caso individual:

The author wishes to express gratitude to Dr. Allan Hurst and staff of the National Jewish Hospital, Denver, Colorado, for the opportunity of studying case material, and to Dr. Jay Arthur Myers of the University of Minnesota for helpful guidance in the preparation of this paper.

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The Technique of Administering Epidural Anesthesia in Thoracic Surgery

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Introduction

Epidural anesthesia has been used successfully in 617 thoracic surgical operations, from October 30, 1945 to August 24, 1949, at the Missouri State Sanatorium at Mount Vernon, Missouri. This paper deals with the technique of administering epidural anesthesia, which the surgical staff of this hospital has found to be most advantageous. It is written because of the many inquiries received following the publication of the first paper in February 1948, and in order to re-evaluate our later results.

Epidural or extradural analgesia is secured by the introduction of the analgesic drug into the epidural space (Fig. 1). This space lies between the dura mater of the spinal cord and the bony and fibrocartilaginous boundary of the vertebral column and extends the full length of the vertebral column. It is closed above by the fusion of the lining of the vertebral canal and the dura mater at the foramen magnum. It is closed below at the sacrococcygeal juncture. Laterally, the space communicates with the paravertebral tissue wherein lie the roots of the spinal nerves and the sympathetic ganglia (Fig. 2). A negative pressure exists within the space, and this factor is a great aid in administering the anesthetic, as will be seen later.

The anesthesia produced is predominantly sensory. Thus, there is no impairment of the intercostal muscles, diaphragm, or the accessory muscles of respiration. Sympathetic paralysis is almost as intense with epidural anesthesia as with intrathecal analgesia. However, the anesthetic does not reach the subarachnoid space nor can it reach the vital centers in the medulla.

Epidural anesthesia has been used only occasionally throughout the world. It was first used by Fidel Pages of Spain in 1920. Some other physicians who have reported its use are: Dogliotti of Italy, Gutierrez of Argentina, Vasconcelos of Brazil, and Dawkins of England.

Advantages of Epidural Anesthesia in Thoracic Surgical Cases

1) The cough reflex is preserved. This one factor is most important in the prevention of postoperative spreads and reactivations, atelectasis, and aspiration pneumonias. The bronchopulmonary secretions are constantly evacuated by preservation of the cough reflex and expectoration.

2) There is maximum oxygenation of the cardio-respiratory system, with minimum deviation from the normal physiology during surgery.

3) It is non-inflammable, so the electric cautery can be used with much more safety than is possible with general anesthesia.

4) Paralysis of the thoracolumbar sympathetic nervous system outflow constitutes the same advantage as is found in spinal analgesia. As a result of this, the body remains warm and dry, with a minimum of fluid loss, thus preserving its normal electrolyte balance. Blood loss at surgery is replaced immediately by an intravenous blood transfusion which is started preoperatively in the greater saphenous vein just superior to the medial malleolus.

5) In our experience there is less loss of blood and less capillary bleeding when using epidural than with other types of anesthesia.

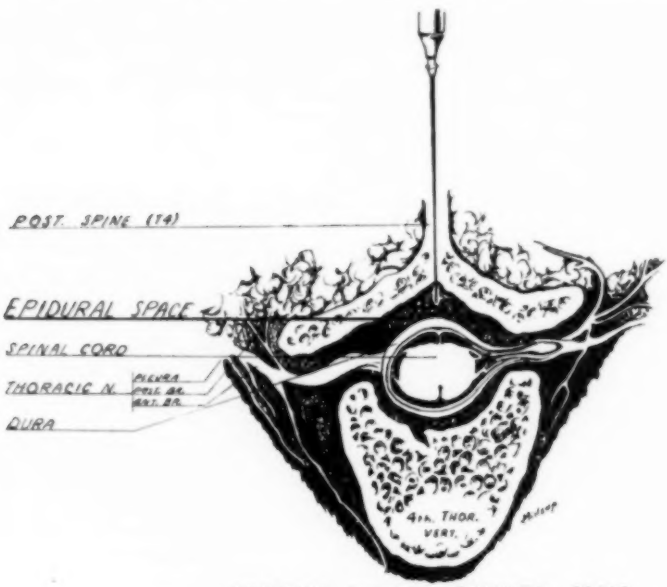

FIGURE 1

6) All types of thoracic procedures can be done using epidural anesthesia. Of the 617 cases reported, there were 397 thoracoplasties, 64 pneumonectomies, 48 plumbage with acrylate pack, 58 lobectomies, 12 thoracotomies, 10 revisions, none decortications, six open pneumonolyses, two rib resections, two closures of broncho-pleural cutaneous fistulae, two Schede operations, two excisions of tuberculoma, one scapulectomy, one lobectomy and thoracoplasty combined, one excision of sinus, one Monaldi operation, and one pericardial cystectomy.

7) The concentration of the anesthetic after the introduction into the epidural space is such that there is a maximum of sensory analgesia and a minimum of motor paralysis.

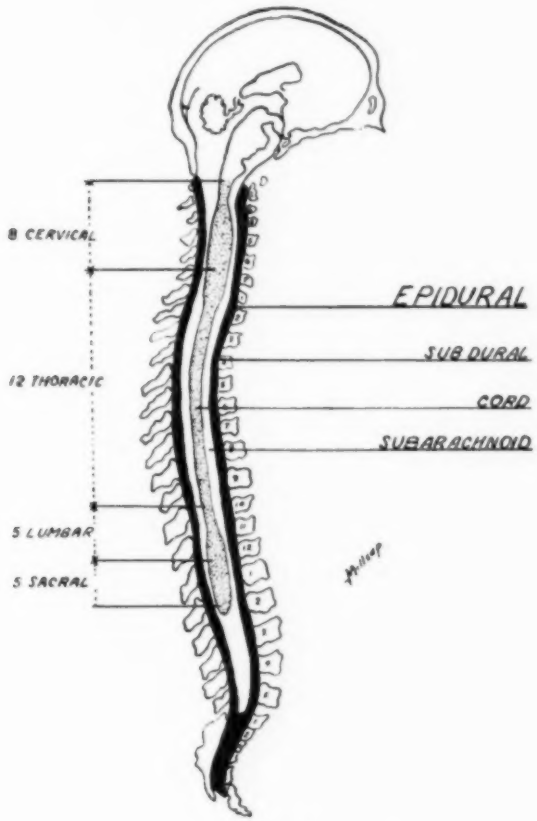

FIGURE 2

8) The epidural space is limited at the foramen megnum and the analgesic solution can not reach the medullary centers.

9) The drug is not introduced into the subarachnoid space where the nerve roots and cord are unprotected.

Nitrous oxide anesthesia was used as a supplementary 33 times. As a rule it was used during the last 10 to 20 minutes of the operation and it was usually given as more or less of an experiment than according to the actual needs of the patient because we were interested to find out if the patient could tolerate a general anesthesia in addition to the epidural anesthesia.

The cases in which supplementary N_2O were used were: 13 first stage, six second stage, five third stage, and one fourth stage thoracoplasties, two extrapleural pneumonolysis with plombage, three lobectomies, two pneumonectomies and one decortication. Local novocain anesthesia was used twice supplementing a first and a second stage thoracoplasty. There was no case of depressed respiration or permanent nerve damage.

Disadvantages of Epidural Anesthesia in Thoracic Surgical Cases

1) The technique of administration is somewhat difficult and many physicians are not familiar with its use. This obstacle can easily be overcome by observing someone familiar with the technique and by experience with the procedure.

2) The psychic factor of being operated upon while awake must be considered from the patient's viewpoint. However, this factor is reversible, as a large percentage of patients are fearful of going to sleep during surgery. The psychic factor of being fearful of being operated while awake can be minimized by the usual preoperative barbiturates and by explaining the advantages of this procedure to the patients.

3) Novocain and pontocaine sensitivity has been a minimal factor, and we attribute this to the preoperative skin testing.

Preoperative Medication

A good barbiturate preparation should be used the night before surgery and again two hours before surgery. We have found grains $1\frac{1}{2}$ to 3 satisfactory. No atrophine preparation is used preoperatively. In our early cases we gave morphine sulphate grains 1/6th before surgery. This practice was discontinued because we found that morphine sulphate grains 1/8th intravenously could be used very advantageously in some cases which required over three hours of operating time.

All patients were skin tested the day before surgery to determine their sensitivity to novocain and pontocaine. A positive pontocaine

reaction would contra-indicate its use. A positive novocain reaction would contra-indicate epidural anesthesia. Therefore we experienced no allergic drug reactions.

Preparation of the Anesthetic

The following equipment is needed upon the anesthetic tray:

Cotton ball sponges.
2—2 ounce beakers or medicine glasses.
1—1 ounce medicine glass.
1—10 cc. syringe.
1—No. 18 guage spinal needle with a short, dull bevel.
1—No. 18 guage plain needle.
1—No. 25 guage plain needle.
1—drape with a four inch opening.
Ampules of novocain and pontocaine with a file.

About 60 cc. of normal saline is placed in one of the larger beakers and 5 cc. of 1 per cent procaine in the small medicine glass. Twenty-eight cc. of normal saline is measured into the second large beaker and 500 to 600 mgs. of novocain is added. The exact amount depends upon the length of the operation anticipated. Twenty to 40 mgs. of pontocaine is also added according to the length of the anticipated surgery and 0.5 cc. of 1-1000 adrenalin is then added to the mixture. This solution should appear clear. Cloudy solutions were obtained a few times and they were discarded because of fear of cnotaminants from the agents used or from the disinfectants used in cleaning the glassware. This mixture should give satisfactory anesthesia for at least three hours.

A simple method of distinguishing the anesthetic agent from the saline solution on the table is to drop the empty novocain ampules into the saline beaker. This procedure will eliminate the chance of confusing the saline with the anesthetic agent.

Administration of the Anesthetic

The patient is placed in the sitting position with the feet over the side of the operating table. The back should be bowed backwards and the neck should be flexed. The patient's head should rest upon an assistant's shoulder (Fig. 3). This position facilitates the location of the spinous processes, especially in the more obese patients. It may also help to create the potential negative pressure in the epidural space.

The factors determining the exact interspace to be used vary with the operation to be performed and the ability to locate the epidural space. The space between the spinous processes of the seventh cervical and the first thoracic vertebrae seems to be

superior for first stage thoracoplasties and extra-deural apicolysis. However, injections as low as the third thoracic interspace have given satisfactory results. For pneumonectomies, lobectomies, and second and third stage thoracoplasties the lower interspaces are preferred. The first thoracic interspace is the easiest to enter because it requires a less acute vertical angle and it is also a wider interspace.

A small skin wheal with one per cent procaine is made in the exact midline in the depression between the spinous processes, using the No. 25 guage needle. The subcutaneous tissue is then injected with procaine to the full length of the needle. The No. 18 guage needle is then used to enlarge the skin opening of the No. 25 guage needle. A surgical knife could be used for this procedure if so desired. However, we feel that this produces more skin bleeding. The short beveled spinal needle is then introduced through the skin opening. The stylet should be left in situ. The needle should be parallel to the spinous processes of the interspace selected. The various structures penetrated are recognized by their differences in resistance. There is moderate resistance felt in penetrating the supra-spinous ligament, slight in the inter-

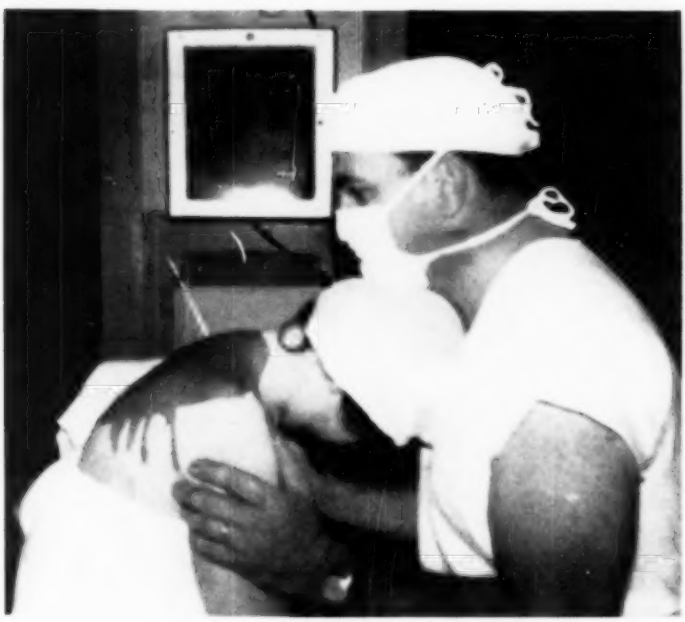

FIGURE 3

spinous ligament, and a marked resistance is felt at the tough ligamentum flavum. When the needle point encounters the tough ligamentum flavum, the stylet is removed and a drop of saline is placed within the hub of the needle. From this point forward the needle should be advanced very slowly, with the operator's fingers resting against the patient's back so that the needle can be steadied. As the needle penetrates the ligamentum flavum, there will be a definite drop, which sometimes is almost a snap. The needle must be checked at this point as the epidural space has been entered. The drop of saline will be sucked into the epidural space. Several drops of saline are placed within the hub of the needle to recheck the "drop sign." If the "drop sign" is not observed at once, two or three cubic centimeters of normal saline are injected to push the dura away from the point of the needle. If the saline goes in easily, an attempt to aspirate spinal fluid or blood is made. If this test is positive, the needle is immediately withdrawn. If the test is negative, another drop of saline is placed within the hub of the needle, and the "drop sign" is usually then observed, due to the negative pressure within the spidural space.

These tests indicate proper location within the epidural space, so 100 cc. of the anesthetic solution is then slowly injected. The patient will usually complain of pain in the back, arms shoulders, or chest after the first 5 cc. of fluid is injected. This sign is also indicative of proper location of the anesthetic fluid. A pause should be made between each 10 cc. of anesthetic injection to allow for dissipation of the solution through the epidural space and paravertebral tissue. As this occurs, negative pressure will again be indicated by the fluid in the hub of the needle being sucked in. Ephedrine sulfate $^3/_8$ to $^3/_4$ grains or an equivalent dose of methedrine is given subcutaneously after the first 10 cc. of the anesthetic is given. The remaining 20 cc. of the anesthetic solution is then given and the patient is placed upon the table with the operative side down for 10 minutes in order to take further advantage of the gravitation of the fluid. In all, 30 cc. of anesthetic solution is injected into the epidural space.

SUMMARY AND CONCLUSIONS

1) The important anatomical and physiological factors of the epidural space are discussed.

2) The advantages and disadvantages of epidural anesthesia are presented.

3) A brief history of epidural anesthesia is given.

4) A detailed presentation is given of the technique of adminis-

tering epidural anesthesia as was used in 617 thoracic surgical cases at the Missouri State Sanatorium at Mount Vernon, Missouri from October 30, 1945 to August 24, 1949.

RESUMEN Y CONCLUSIONES

1) Se discuten los factores anatómicos y fisiológicos importantes en el espacio epidural.

2) Se presentan las ventajas y desventajas de la anestesia epidural.

3) Se hace una breve historia de la anestesia epidural.

4) Se describe con detalle la técnica de la epidural tal como se ha usado en 617 casos de cirugia torácica en el Sanatorio del Estado de Missouri en Mount Vernon, Missouri, de Octubre 30 1945 a Agosto 24, 1949.

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Mesothelioma of the Pleura

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History

Wagner[1] in Germany in 1870 was the first to describe a tumor with the characteristics of a pleural mesothelioma and to recognize it as a pathological entity. He called it "a tubercle-like lymph adenoma." From the time of this first description there has been a controversy among medical authorities until recently relative to the origin, histology and nomenclature of this disease. It has been variously called pleural carcinoma, mesothelioma, endothelial carcinoma, mesothelial carcinoma, endothelioma, carcinomatodes, adeno - endothelioma, sarco - endothelioma, perithelioma, lymphangio - endothelioma, fibro - endotheliosis of pleura, lymphangitis proliferans and Cornil[2] and his co-workers in France have suggested the name, pleuroma.

Although there have been many opinions, some authors even denying the existence of a primary pleural neoplasm, the names have narrowed down until the most common ones in use are: 1) Endothelioma, by those who believe the tumor originates from the endothelium of the pleural lymphatics and 2) Mesothelioma, by those who maintain the tumor originates from the lining epithelium of the pleura, since the latter are derived from the mesoderm in the embryo.

Ewing[3] as late as 1940 states: "It is possible that two groups of serous endotheliomas should be recognized, one invasive with metastases and derived from the endothelium of the lymph spaces and another superficial, nodular or papillary, and originating from the lining cells."

The confusing elements in the tumor seemed to be the mixture of epithelial appearing cells and connective tissue. The epithelial appearing cells at times arrange themselves as, and take on, glandular characteristics. The connective tissue stroma varies in amount and density and shows areas of hyalinization. How could a cell which is primarily epithelial in nature take on glandular and connective tissue elements?

Maximow[4] demonstrated in 1927 that the covering cells of the serosal surfaces are pleomorphic and when cultured outside the body, in vitro, assume a fibroblastic nature and form collagen fibres. Twenty years later Maximow and Bloom[5] stated, "The mesothelium is a simple, squamous cell layer which covers the

surface of all the serous membranes (peritoneum, pericardium, pleura). Its elements have the classical structure of true squamous epithelial cells. The prospective potencies of these elements are of dual nature—epithelial and fibroblastic. In tissue cultures the mesothelium of mammals may show for a certain time a purely epithelial type of growth in islands and sheets of polyhedral flattened cells. Tumors of epithelial character may develop from the mesothelium and, possibly, structures similar to uterine glands. On the other hand, in inflammation the mesothelial cells, after a period of contraction and of rounding off, finally give rise to typical fibroblasts, i.e. to connective tissue cells. The same occurs in tissue cultures. They are never transformed into ameboid phagocytes."

Young[6] has shown that the pleural serosal cells of rabbits can undergo extensive hyperplastic and metaplastic proliferation, forming gland-like spaces lined with swollen epithelial-like cells.

Boyd[7] now summarizes tumors of the pleura as "primary and secondary. The former are rare, while the latter (metastatic carcinoma) are fairly common. Primary tumors may be divided into two main groups, localized and diffuse. Localized tumors are of many histological types, but have one characteristic in common, in that they arise from the tissues beneath the surface lining of the visceral or parietal pleura, while the diffuse tumors arise from the surface lining, and are commonly known as an endothelioma. They would be better called mesothelioma, as the surface cells are mesothelial in character, the lining of the pleural cavity being derived from the coelomic epithelium, which in turn is developed by splitting of the mesoderm.

The diffuse tumor may present characteristics of either epithelial or connective tissue due to the varied potentialities of the mesothelial cells. Microscopically the tumor consists of large spherical cells arranged in solid masses and columns, often within the lumen of lymphatics they may have a definite glandular formation as in adenocarcinoma. The stroma is usually fibrous and abundant."

Case Report

F.M., a 62 year old male passenger from France was admitted to the hospital January 8, 1949. He complained of cough, profuse expectoration, shortness of breath, pain in the left side of the chest, weakness and hoarseness. His past history was irrelevant, except that he had a dry cough for a number of months before departure from France 10 days before. Shortly after departure he developed a cold and his cough became worse. At this time he began to expectorate a great deal, his throat felt tight and he became hoarse.

Physical examination: The patient was an undernourished, small male, who appeared acutely ill. He was hoarse and dyspneic and coughed fre-

quently making a loud, hollow sound. His temperature was 100 degrees F., pulse 90, respirations 30 and blood pressure 105/80. His color was good. Examination of the head, including the eyes, ears, nose, pharynx and tongue was negative. He had many loose and carious teeth. The thyroid gland was normal in size and consistency. There was a round medium soft mass about the size of a hazelnut in the left anterior triangle of the neck, just above the medial portion of the left clavicle and under the distal end of the sternomastoid muscle. The trachea was in the midline.

The chest was symmetrical in form, but the expansions were abnormal, the left being greatly diminished and the right increased above normal. On the left side of the chest high-pitched bronchial breath sounds were heard over the upper lobe, with frequent rhonchi, and loud moist rales over the distal half of the chest posteriorly. Voice sounds and tactile fremitus were diminished, and there was marked dullness to precussion throughout the entire left side.

The right chest findings were normal. The abdomen showed a fullness in the upper part with no tenderness or masses. The skin, extremities and prostate were normal. The neurological examination was negative. The left vocal cord was paralyzed.

Laboratory findings: Sputum smears and cultures for acid-fast bacilli were negative. Other organisms found in the sputum were streptococcus, staphylococcus and pneumonococcus. The red cell count was 4,000,000 per cu. mm., hemoglobin was 80 per cent (Sahli) and the white blood cell count was 15,100 per cu. mm. The differential count showed 76 per cent neutrophiles, 1 eosinophiles, 19 small monouclear lymphocytes, 1 large mononuclear lymphocytes, and 3 per cent transitionals. The urine showed no abnormality. Serological tests for syphilis were negative. The sedimentation rate was 30 mm. in one hour (modified Cutler). A chest x-ray film showed (Figure 1) a rather homogeneous haze in the upper two-thirds of the left lung field. There were mottled densities in the lower third of the lung field and a round density measuring approximately 3 cm. in diameter in the lateral apsect of the left base. The left half of the diaphragm was smooth. There was slight blunting of the left costo-

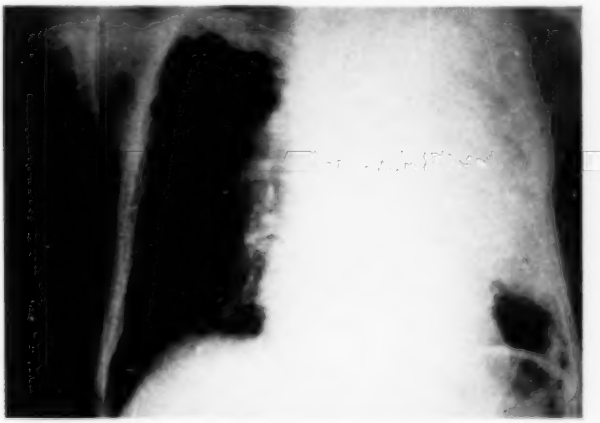

FIGURE 1

phrenic sinus. The trachea was approximately in the midline. The right lung field was clear and the right half of the diaphragm was smooth. The right heart border was normal in appearance. The left border was obscured by adjacent pulmonary densities.

A tentative clinical diagnosis of inoperable neoplasm of the left lung with secondary infection was made. Following administration of 40,000 units of penicillin every three hours for a few days, his breathing was less labored and he attended to his own personal hygiene. His appetite improved and he had less pain in the chest, but weakness continued and his temperature continued to spike to 102 degrees F. He had a loud deep-toned cough and expectorated about six ounces of white muco-purulent sputum a day. Papanicalaou stains of sputum on two occasions were negative for malignant cells.

On January 19, 1949 more chest x-ray films were inspected. The lateral projection revealed a multi-lobulated mass in the upper two-thirds of the left lung field, which extended from the posterior through the middle into the anterior part of the chest.

On January 19, 1949 an 18 gauge needle was passed into the left sixth intercostal space in the posterior axillary line. The needle at full length could be moved in all directions without meeting resistance. There seemed to be a pleural space but no fluid could be aspirated, only air. The plunger of the syringe was withdrawn without resistance. The manometer was attached, but the reading was zero. No biopsy was done because no solid tissue was found.

On January 21, 1949 an 18 gauge needle was passed into the left sixth intercostal space in the mid-axillary line and 2 cc. of iodized oil and 5 cc. of 1 per cent solution of gentian violet were injected. No dye was ever seen in the sputum.

The patient's condition gradually became worse; he did not seem to have much pain, but he became weak, cyanotic, with fast and weak pulse and he expired on January 30, 1949 after 22 days in the hospital.

Pathology

The necropsy was performed by Dr. Louis Winkelman. The body showed evidence of recent weight-loss. The skin was clear. The gross findings were limited to the left thorax. The left lung was atelectatic and retracted from the chest wall in the lower two-thirds. The upper third of the lung was adherent to the chest wall and there was about 300 cc. of brownish fluid in the pleural cavity.

The pleura overlying the left lung was strikingly white and markedly thickened. It was 1 cm. thick on the lateral wall and at least 2 cm. in the interlobular fissure, moderately firm in consistency and exuded a whittish-grey fluid on pressure. This abnormal pleura extended over the apex and inferiorly towards the lower lobe, where it appeared normal.

On removing the lung from the chest it was found that the parietal pleura over the apex was involved and fused with the visceral pleura. These were fused with four lymph nodes in the superior aperture of the thorax and lower part of the neck. The

thickened pleura in other parts of the chest fused with large firm white lymph nodes in the hilar region, and could not be removed from these nodes. The thickened pleura was peeled from the apex and lateral surface of the lung. Although the pleura was smooth on its outer surface, the inner surface was nodular and indented the lung at numerous points as much as 2 cm. in depth. The lung was sectioned and the bronchial nodes were large and white.

The right lung was normal in appearance and consistency. All other organs were essentially normal. No metastases were found.

Microscopic examination showed that the pleural tumor was composed of two types of tissue, which followed a definite pattern. Varying sized nests of epithelial-like cells were seen enclosed within strands of connective tissue stroma (Figure 2). These cells were markedly basophilic, their nuclei varying from ovoid to round in shape. They often contained prominent nucleoli, occasional mitotic figures, and little cytoplasm. In some instances, a nucleus made up the entire cell, so no cytoplasm was seen. These cells were not arranged in any definite pattern and showed no signs of polarity. The connective tissue showed strands of collagen fibers and some hyalinization (Figure 3).

Sections of the bronchial, tracheal, and cervical lymph nodes showed a characteristic appearance. The architecture of the lymph follicle was still maintained, but by far the greater portion of the lymph follicle was replaced by malignant cells. A few tumor cells

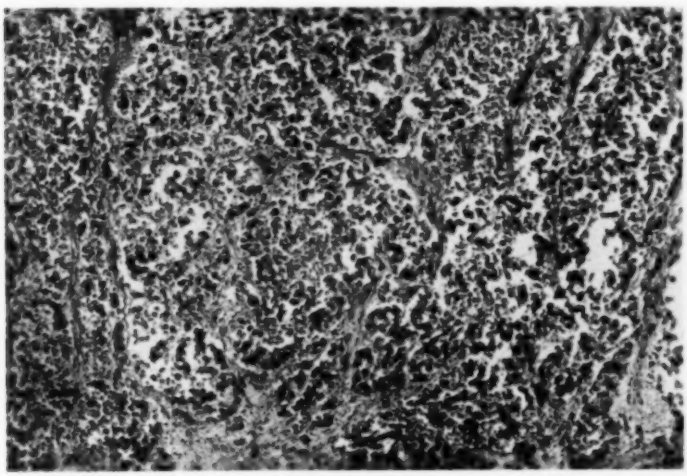

FIGURE 2

had entered the bronchial muscles, but they were not distorted. Malignant cells were seen to reach the bronchi.

In some areas of the lung lymphatics the picture of necrosis and secondary infection was present, and there were few nests of discernible malignant cells. An unusual feature was seen in some of the sections, especially near the hilar region. Here irregular dark blue staining non-cellular areas were present. Those appeared to represent heterotopic calcification, a feature occasionally seen in endothelioma and described as osteoid production. The remainder of the lung showed areas of atelectasis and bronchopneumonia. No tumor cell was seen in the lung parenchyma.

Pathological diagnosis: Endothelilioma of the left pleura with involvement of the left bronchial, hilar, and cervical lymph nodes.

Discussion

Every case of mesothelioma of the pleura that has been reported in the literature has been fatal. It is a rare malignant neoplasm occurring in about 1.1 cases per 1000 necropsies, and it occurs most frequently between the ages of 40 and 60 years. The right and left pleura are affected with equal frequency, but the rates of females to males are 1:1.8 according to Saccone and Coblenz.[5]

Clinical signs and symptoms as explained in the literature are most confusing. The onset of the disease is described as gradual, its duration is from six to nine months, only rarely over two years

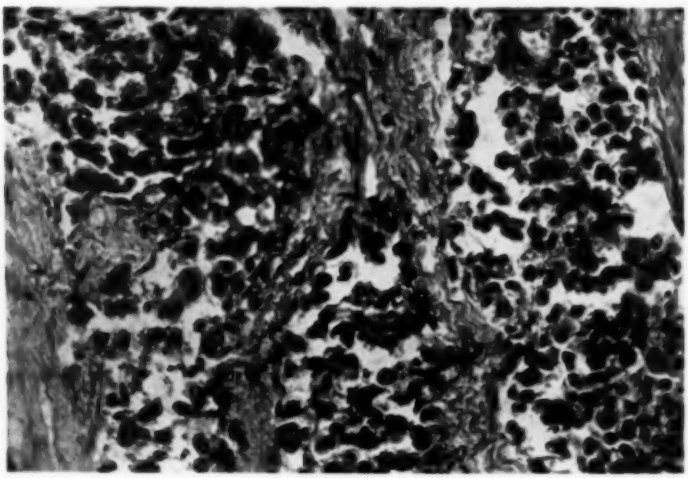

FIGURE 3

from the time of recognition. Our case and the one presented by Coulter[9] was more rapid.

Cough seems to be a constant symptom. At first it may be dry and mild, and may remain this way throughout the course of the disease. The cough may, however, become hard, frequent, and produce a hollow sound. Stridor may develop due to the gradual pressure on and obstruction of the bronchi. Expectoration may be moderate, sometimes gelatinous in nature, depending upon the extent of the disease. In our case the expectoration was profuse, heavy, white, muco-purulent because of the secondary infection. Sputum is not blood-streaked and hemoptysis is not the rule.

The temperature is usually normal. Where there is a secondary infection, as in our case, it will rise depending upon the severity and extension of the infection. Banyai and Grill[10] presented a case with irregular, remittent fever, not unlike that seen in pulmonary tuberculosis. Our case was similar. Penicillin gave some temporary relief. Pain is pleuritic in type and may be severe over the affected side. Our case was similar in this respect to the one described by Coulter.[9] There was little pain even with the secondary infection.

Dyspnea seems to be a constant symptom. It was severe in our case. The disease binds the lung with a constricting action, and prevents proper expansion. The elasticity of the pleura is gone. Expanding and enlarging lymph nodes produce obstruction of the bronchi with resulting obstructive emphysema and finally atelectasis. The function of the lung is lost and pulmonary insufficiency is pronounced. In our case the expansion of the chest wall on the affected side was greatly diminished. After our case received penicillin a few days, dyspnea became temporarily improved. The infection was apparently adding to the pulmonary insufficiency. Although the right lung was not involved cyanosis developed toward the last. His appetite remained fairly good until a few days before death. No other system seemed to be greatly affected by the disease; however, he may have been developing cor pulmonale.

Pleural effusion is given as one of the first signs in most of the cases reported. X-ray inspection of the chest gives a picture of pleural effusion although there may be no fluid. The thickened pleura is radio opaque. In our case the film showed a haze, except over the lateral part of the left base. Coulter[9] found fluid and replaced it with air so as to obtain better x-ray visualization of the tumor. He recovered malignant cells from the fluid. Dyspnea was not relieved by aspiration and fluid reformed quickly.

A diagnostic feature according to Weisman[11] is that the aspirating needle encounters great resistance in passing through the pleura. In our case, on two occasions a number 18 gauge needle

met no resistance. A biopsy of the node on the anterior triangle of the neck would have revealed the pathology as this node (when removed at necropsy) had the same structure as the bronchial and hilar lymph nodes. Papanicalaou stains may show malignant cells in the sputum, as this neoplasm does break into the bronchi.

There may be clubbing of the fingers and unilateral or bilateral vocal paralysis. Banyai and Grill[10] described a condition of gradual compression of the larger thoracic veins, which was manifest by the appearance of dilated and enlarged skin veins over the abdomen on the same side, which carried the blood in reverse from the chest indirectly to the inferior vena cava.

X-ray inspection may not be helpful in the early stages when findings suggest pleural reaction with or without fluid. The aspiration of fluid and induction of artificial pneumothorax may aid diagnosis. It may show multiple smooth tumors, nodules of various sizes, and thicknesses. A small amount of iodized oil may help and gentian violet may determine whether broncho-pleural fistula is present. Later, the x-ray film may show evidence of markedly collapsed lung with atelectasis, displacement of the heart, shift of the mediastinum, enlarged hilar and mediastinal lymph nodes. The diaphragm may be affected, becoming immobilized and frequently depressed. Pulmonary abscess may develop from secondary infection.

Laboratory findings are not consistent. Anemia may or may not be present. The hemopoietic system may respond to the anoxia with increase in the number of red blood cells. The red cell sedimentation rate is increased. It is usually increased in pulmonary tuberculosis and pulmonary neoplasms.

Bronchoscopy will probably not be helpful in the early stages. It might show bronchial obstruction later, due to the enlarged lymph nodes. Exploratory thoracoscopy, however, should reveal the tumor. Sauerbruch[12] states, "it is just as reasonable to establish a diagnosis in the chest by exploratory operation as it is to explore the abdomen." Biopsy of enlarged nodes near the tumor or even far from it may reveal the type of tumor.

Treatment is usually symptomatic. Deep x-ray irradiation has been tried, and found ineffective. Surgery may be of some avail if an early diagnosis could be made. There is no evidence to show that any of the drugs or radioactive substances used against neoplasms have been administered in this disease.

The findings at necropsy are fairly characteristic. There is the white thick evenly distributed pleura with nodular formation with metastases to the bronchial, axillary, cervical, mediastinal and retroperitoneal lymph nodes. The lung is not involved, but compressed and atelectatic. Cases have been reported showing metas-

tases to the brain, kidney, adrenals, thyroid, bone and Stout and Murry[13] had a case where the malignant cells infiltrated the head of the pancreas and right ovary. In most cases, however, there is lymphatic infiltration, and little disturbance of other tissues.

Microscopic findings are less specific, but should be easily interpreted by a competent pathologist. The carcinomatous and sarcomatous elements in one tumor may be confusing. The tumor cells may vary from medium size, round to large, polygonal and medium-sized columns and are arranged in nests and broad sheets within connective tissue stroma. They may take the form of adenomatous tissue. The cytoplasm and chromoplasm of the tumor cells stain acidophilic and large nuclei are seen, but mitotic figures are often wanting.

SUMMARY

A case of mesothelioma of the pleura is presented together with a discussion of the clinical aspects of this disease.

RESUMEN

Se presenta y se discute un caso de mesotelioma de la pleura.

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The Technique of Bronchospirometry*

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Introduction

The increasing application of major thoracic surgery to the problem of pulmonary tuberculosis with bilateral involvement, and to the treatment of non-tuberculous diseases of the lung in older patients and in those with contralateral complicating disease has stimulated the increasing use of bronchospirometry. This article is an attempt to describe a simple, safe and practical technique for the use of the Zavod[1] catheter, which the senior author has used for more than 10 years.

Four independent workers have made the most significant contributions to the study of the function of each lung separately. Jacobaeus[2] in 1932 described a double lumen rigid bronchoscope with which the first studies were done. Soft double lumen catheters were designed independently by Gebauer[3] in 1939 and Zavod[1] in 1940. They differ only in that the Zavod catheter has two capillary channels for inflation of the cuffs, permitting different pressures in each, while the Gebauer catheter has a single channel through which both cuffs are inflated. An entirely different catheter has been designed by Norris and co-workers,[4] which has a single lumen and cuff. The reports of diminished occlusion by secretions and of lessened stenosis effect encourage its trial.

Since the development of the Zavod catheter, great strides have been made in obtaining knowledge of the effects of surgical procedures and disease states on the functional capacity of the lungs. Numerous improvements in the technique of bronchospirometry have also been made, with particular reference to the topical anesthesia.

Equipment

1) Bronchospirometry catheter, Zavod type. (Deterioration of the rubber is rapid; if any volume of work is done, at least four or six catheters should be on hand).
2) Stilet built for the catheter.

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3) Two mercury manometers, to read pressures up to 26 cm. of mercury. (Used to measure pressure in cuffs).
4) Two 10 cc. Luer-Lock syringes.
5) Two glass adapters. (To connect catheters to recording apparatuses).
6) Two spirographs; nine liter large Benedict-Roth type spirographs with ventilograph attachments to record minute volume are desirable,[5] but basal metabolism recorders can be used.
7) Pontocaine solutions, 2 per cent and ½ per cent. These should be made fresh.
8) Pentothal sodium ampules (or sodium amytal); a syringe containing an adequate dose should be ready in case signs of pontocaine toxicity appear.
9) De Vilbiss spray bottle.
10) Laryngeal mirror.
11) Laryngeal forceps.
12) Laryngeal cannula.
13) Room with fluoroscope, preferably a fluoroscopy table.

Preparation of Equipment

All the equipment is prepared before the procedure is started. Several of the previously sterilized bronchospirometry catheters are inspected for leaks and the cuffs are inflated with air under pressure measured by the manometers, and the pressure causing the desired cuff diameter is recorded. The metabolism machines are filled with oxygen and tested for leaks. The anesthesia equipment is set up in the fluoroscopy room. Although to date we have had no reactions from the use of pontocaine, we recommend that sodium amytal or pentothal be prepared before each bronchospirometry for immediate use should the need arise.

Preparation of the Patient

Every patient undergoing bronchospirometric studies has had spirometric tests one or several days before. The patient has taken no food for four hours prior to the intubation. Pentobarbital 0.1 gm. is given orally one hour before the bronchospirometry. Atropine sulfate 0.6 mgm. is given subcutaneously so timed that about 20 minutes elapse before the actual intubation. Proper timing of the atropine is essential if its full effect is to be obtained at the time when it is most needed. One should allow 12 to 15 minutes for a careful topical anesthesia.

Anesthesia

A two per cent solution of pontocaine is used for the upper airway and a one-half per cent solution for the trachea and

bronchi. Good visualization of the larynx is essential. The patient holds his tongue with gauze and is told to breathe normally. He is instructed to spit out all excess solution after each application. Three steady squeezes of the bulb of the Vilbiss spray will apply an even coating of the solution to the tonsillar area, uvula and posterior pharyngeal wall. A waiting period of 30 to 45 seconds permits this to take effect, while the patient is clearing out excess solution. The application is then repeated. If after the second waiting period there is any gag reflex from the uvula, a third application is made. The nozzle of the spray is then directed downward and with three or four squeezes of the bulb the spray is directed to the epiglottis, vocal cords, and pyriform fossae. The patient is then questioned as to any symptom of toxicity, such as dizziness or nervousness. The operator meanwhile wraps the grasping end of the laryngeal forceps with cotton and soaks it in the 2 per cent solution. The excess solution is squeezed out and, with mirror visualization, the tip is placed in one pyriform sinus and then in the other. With a laryngeal cannula a few drops of the 2 per cent solution are allowed to fall on the vocal cords with the patient singing "ee-ee." The patient is then tilted to one side, his head straightened, and one and one-half cc. of the one-half per cent solution of pontocaine is slowly dropped from a laryngeal syringe through the vocal cords into the trachea. This is repeated with the patient tilted to the opposite side. The solution is dropped at the beginning of a deep inspiration. A cough may result which should be encouraged. It is important to apply the tracheal anesthesia to both sides. When the bronchospirometry catheter is in place and the cuffs inflated, pressure is exerted all around the trachea; if cough and sense of discomfort is to be avoided, the entire circumference of the trachea should be anesthetized. Another reason is that at times it is technically impossible to intubate the left bronchus and the right must be intubated. With the right side previously anesthetized one is prepared for such an occasion.

Intubation

The bronchial end of the catheter is bent approximately to the same angle as that between trachea and left main bronchus. The flexible steel stilet is inserted into the lumen of the catheter with a drop of lubricant. We have performed successful catheterizations without stilet as suggested by Baldwin and co-workers,[6] and we believe the choice is a personal one. For the intubation the mirror is held in the left hand and the catheter in the right. The patient holds his tongue with gauze. He is warned that he may feel slightly short of breath for the first few seconds. The

catheter is manipulated so that the tip is just above the vocal cords; the mirror is set aside. With the left hand the stilet is withdrawn while the right hand rapidly advances the catheter between the cords down into the trachea. Then the patient is instructed to hold the catheter close to his lips and not to bite, and he lies down on the fluoroscopy table. The catheter is advanced under fluoroscopic guidance until its radiopaque tip is about three cm. within the left main bronchus. In this position the inflated cuff will occlude the main bronchus but not the lobe orifices. Figure 1 shows the catheter with the inflated cuffs in the correct anatomical position. When the catheter is properly positioned the manometers and the recording machines are attached. A note is immediately made as to which machine is recording which lung. The cuffs are inflated to pressures previously found necessary, and the recording machines are turned on. During quiet breathing there should be a slight oscillation of the mercury levels in the manometers; this is evidence that the cuffs occlude the space between the catheter and the wall of trachea and bronchus, respectively. Constant observation of the recordings is maintained so that a leak in the system is promptly recognized. A thread of gauze held close to the patient's mouth will flutter if the tracheal cuff is insufficiently inflated. At the end of a six minute recording several vital capacity re-

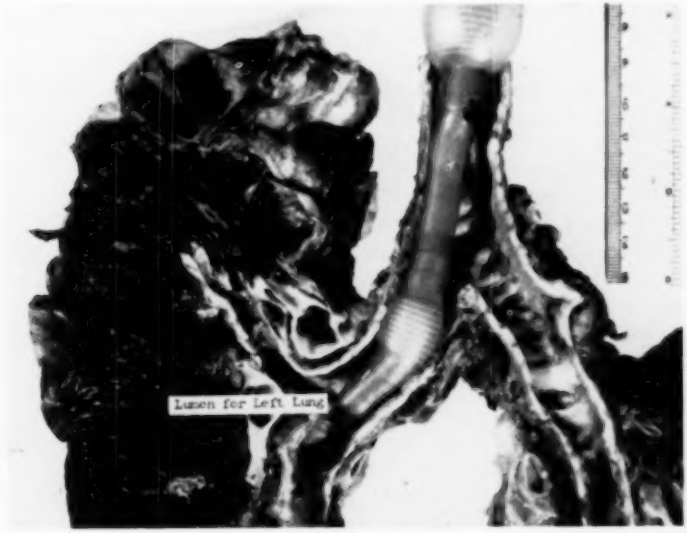

FIGURE 1: The catheter in correct anatomical position, the cuffs are inflated.

cordings are taken. For these the patient is instructed to take a maximum inspiration followed by a *slow* complete exhalation (a rapid exhalation will induce a cough). After each vital capacity recording a quick calculation is made to determine how close the sum of the two lung recordings approaches the total vital capacity found by spirometry. If the difference is less than 10 per cent it may be assumed that no branch bronchial orifices have been occluded. If the vital capacities do not add to within 10 per cent of the vital capacity found by spirometry, it is our practice immediately to test for leaks and then re-fluoroscope the patient and check the position of the catheter. If the position is possibly improper, the cuffs are deflated and the catheter re-positioned. If the catheter is moved with the cuffs inflated a terrifying sensation of asphyxia is induced. The cuffs are reinflated and additional vital capacity recordings are taken. If satisfactory values are obtained a record of quiet breathing is again taken. Bronchial secretions usually become manifest by a gurgling sound in the catheter if too prolonged a tracing is attempted. After the desired record has been obtained the spirometers and manometers are disconnected; the patient is instructed to sit up, and the catheter is withdrawn. If there is any question of blockage of a catheter channel by mucus, water is run through each lumen. A mucous plug if present can then be demonstrated and the evidence recorded so that the results of the examination will not be misinterpreted. The patient is then instructed to take nothing by mouth until the anesthesia has completely disappeared (usually after two hours). A gargle or mouth wash may be prescribed for the mild sore throat which follows the procedure in a high percentage of cases.

Discussion

The technique described will offer the following data for each lung. Oxygen intake, minute volume, ventilation equivalent, tidal air, vital capacity, complemental air and reserve air. The relation between the complemental and reserve air is altered by the procedure, the midposition being raised by the effect of stenosis breathing. The proportions of each value to the sum of the two are the factors of significance in clinical interpretation of bronchospirometry reports.

The indications for and contraindications to bronchospirometry have been discussed by Pinner and co-workers.[7] Bronchospirometry should be done when irreversible operations on one lung are planned (thoracoplasty, segmental resection, lobectomy, pneumonectomy) when there is any doubt as to the function of the other lung; clinical and roentgenological examinations frequently per-

mit some estimation of the function, but are not reliable and sometimes misleading. The bronchospirometric findings may for instance show whether the patient will be able to stand a pneumonectomy or at the most only a lobectomy.

Contraindications to bronchospirometry are: Tuberculous ulcerations of larynx, trachea or bronchi; high fever; recent hemoptysis; dyspnea. In patients with abundant sputum secretion such as in the presence of bronchiectasis, it is usually not possible to obtain satisfactory records.

The procedure if done carefully is innocuous.

Summary: A technique of bronchospirometry is reported.

Resumén: Se discuta el térnico del broncho-spirómetro.

Thanks are expressed to Drs. James Finnerty and Joseph Coyle for their valuable suggestions regarding the anesthesia and to Dr. Oscar Auerbach for permission to use specimens from the Department of Pathology for photographs. Photography by the Medical Illustration Department.

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Acute Appendicitis Occurring During Therapeutic Pneumoperitoneum*

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Although acute appendicitis has been previously reported in cases receiving pneumoperitoneum for pulmonary tuberculosis, the full appreciation of the seriousness of the condition has not been adequately stressed. There are few references to such cases in the literature. In evaluating the results of pneumoperitoneum therapy, Rilance and Warring cited seven cases of appendicitis occurring in 101 cases of pneumoperitoneum, an incidence of 6.9 per cent. The occurrence of appendicitis in their control group of 2017 sanatorium patients was only 0.64 per cent. They postulated a reason for this high incidence of appendicitis in pneumoperitoneum patients in the poor attempt for natural processes to localize such infection in the air-filled abdomen. On the other hand, according to Moyer who reported on 550 patients with pulmonary tuberculosis treated by a combination of artificial pneumoperitoneum and phrenic nerve operation, the incidence of acute appendicitis was not higher in this group than in his sanatorium patients in general.

Justification for immediate surgery by most surgeons lies in making a diagnosis of acute appendicitis. There are instances, however, when findings are indefinite, and the surgeon adopts a policy of observation. The results of such conservatism are borne by any statistical study of the disease, but surprisingly few fatalities are recorded where the operator recognized the infection in due time and removed the appendix. When pneumoperitoneum is present, the progress of infection appears to be so rapid that one doubts whether conservatism can be adopted safely. Even though the diagnosis may not be certain, the dangers of surgical exploration of such mistaken conditions as hemoperitoneum, tuberculous peritonitis, tuberculous enteritis, and others would seem to be minimal when compared to the certainty of spreading peritonitis if such a case were appendiceal. Although the author has not experienced the outcome of a conservative policy in such obscure cases, the impression gained by the findings in patients

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herein reported would seem to indicate the seriousness of such a policy. One cannot help but be impressed by the rapidity with which the appendiceal infection becomes a general peritoneal one in face of a therapeutic pneumoperitoneum.

Case 1: W.R.A., a 32-year-old white male, was admitted November 16, 1948 with bilateral pulmonary tuberculosis which was predominantly exudative from both apices down to the fourth ribs anteriorly. Streptomycin 1.0 gram daily was started December 2, 1948 for tuberculous laryngitis and continued for 42 days. Therapeutic pneumoperitoneum was initiated April 28, 1949 and refills were given about once every seven days. Suddenly at 4:00 p. m., June 28, 1949, he complained of abdominal pain which soon localized to the right lower quadrant. He was nauseated but suffered no emesis. The oral temperature was 98.4 degrees F. but rose to 100.3 degrees F. by 8:00 p. m. Examination showed marked local tenderness and spasm over the area of the appendix. A leucocyte count revealed 20,500 cells of which 93 per cent were polymorphs.

Appendectomy was performed under 150 milligrams of procaine intraspinally at 11:00 p. m. On opening the peritoneum both air and fluid escaped. There were about 1000 cubic centimeters of thin, turbid, yellowish fluid in the peritoneal cavity. The appendix was swollen, reddened, and covered with a fibrinopurulent exudate and lying free within the cavity. There was no omentum nearby nor evidence of walling-off by any adjacent structure. Appendectomy was performed. Postoperative course was uneventful and pneumoperitoneum was reinstituted three weeks after the appendectomy.

Culture of fluid taken from the peritoneal cavity was sterile. The pathology report showed the appendix to contain a large amount of fibrin and hemorrhage. The wall was thickened and its lumen filled with a purulent material. Microscopically the sections showed marked hypertrophy of the wall with a fairly large lumen. There was an enormous infiltration of polymorphs filling the entire lumen and most of the submucosa. The mucosa was desquamated and there were polymorphs scattered everywhere. *Diagnosis:* Acute appendicitis.

Case 2: W.L.W., a 52-year-old white male, was admitted to this hospital on December 2, 1948 with bilateral pulmonary tuberculosis involving the major portion of both upper lobes. He was placed on therapeutic pneumoperitoneum and streptomycin parenterally 0.5 gram daily on March 23, 1949. Refills of air were given about every three or four days. Suddenly at 5:00 a. m., July 5, 1949 he complained of generalized abdominal distress which localized to the right lower quadrant within two hours. He had eaten some watermelon the night before which he blamed for his symptoms. He was nauseated but did not vomit. His oral temperature was 99.0 degrees F. at 8:00 a. m. Clinical findings were those of moderate tenderness over the right lower quadrant with no evidence of spasm. The leucocyte count at this time was 10,000 per cmm. of which 75 per cent were polymorphs. The examiner was not sure that some process other than acute inflammation was responsible and he was observed further. By 4:00 p. m. his complaint of soreness in the right side was considerably augmented and clinical examination revealed marked tenderness over McBurney's point. The oral temperature was still 99.00 degrees F. but ths leucocyte count rose to 19,000 with 85 per cent polymorphs.

Appendectomy was done under 150 milligrams of procaine intraspinally at 7:00 p. m. On opening the abdomen, both air and fluid rushed out. There were about 1200 cubic centimeters of thin, turbid, yellowish fluid in the peritoneal cavity. The cecum was high and the appendix was lying free within the cavity with marked evidence of suppuration, induration and distention throughout its length. The omentum was nowhere near the organ and there was no adhesive process anywhere about the cecum or appendix. Appendectomy was performed without incident and postoperative course was normal. Pneumoperitoneum was reestablished three weeks after the appendectomy.

Culture of the peritoneal fluid was sterile. The pathologist reported the appendix to contain a large amount of fibrin on the surface. The walls were thick and the proximal end was almost completely occluded. Microscopically there was complete desquamation of the mucosa and the appendiceal lumen completely filled with pus cells, lymphocytes and red cells. Most of the submucosa, muscularis and serosa was obscured by the infiltration of sheets of pus cells, red cells, fibrin and a few lymphocytes. *Diagnosis:* Acute appendicitis.

Both patients showed virtually the same pathological process: An advanced suppurative process in the appendix with little ability or attempt to localize the infection by adjacent surrounding structures. Both appendices were quite free of adhesion formation and the omentum failed to find the inflamed organ. There was an early generalized peritoneal reaction as evidenced by 1000 to 1200 cubic centimeters of thin, turbid, yellowish exudate throughout the peritoneal cavity. Both cases had been fluoroscoped prior to the onset of symptoms when no clinical evidence of peritoneal fluid existed. The duration of symptoms was short for the degree of pathology demonstrated; seven hours in one case and 14 hours in the other.

The degree of spreading peritonitis depends in part on the ability of local inflammatory reaction to wall it off. This defense depends on the well-known factors of phagocytosis, fibrinous exudation and adhesion formation. Delayed defense mechanisms can result in abscess formation if the patient does not succumb to an overwhelming generalized toxemia. It is quite easy to see how such a spreading process can involve most of the peritoneal cavity when pneumoperitoneum is present. The omentum is hardly an efficient barrier in such cases, not only due to space factors but also due to widespread exudation. This exudative process itself is somewhat foreign to the peritoneum and can detract the omentum and other defense processes from the main source of infection. Moreover, the guiding influence of the mesentery and various abdominal folds is fruitless in restraining the general spread of infection.

At this hospital, pneumoperitoneum has been used on 184 patients since July, 1944. These are the first cases of suspected

appendicitis seen since its advent and both occurred within four days of one another. One cannot give an accurate account of the incidence of appendicitis in sanatorium patients as many will not report symptoms to the physician unless conspicuously severe. There were, however, five cases of appendicitis operated from the group of sanatorium patients not receiving pneumoperitoneum, an incidence of 0.15 per cent. This compares with an incidence of 1.08 per cent for the group receiving pneumoperitoneum. The incidence of admissions for appendicitis in the hospital, both tuberculous and nontuberculous, during this study period was 1.23 per cent. While our ratios correspond to those of other authors, we do not find the incidence of appendicitis in pneumoperitoneum subjects any greater than that of general hospital patients. However, the low incidence of appendicitis in hospitalized tuberculous patients remains unexplained.

SUMMARY

1) Two cases of appendicitis occurring during therapeutic pneumoperitoneum are reported exemplifying the rapidity of peritoneal involvement in such patients.

2) The pathological findings in appendicitis in such patients would seem to justify immediate surgical intervention even in those cases where the diagnosis is doubtful.

RESUMEN

1) Se refieren dos casos de apendicitis que ocurrieron durante el tratamiento con neumoperitoneo que muestra la rapidéz de la invasión peritoneal en semejantes casos.

2) Los hallazgos patológicos en tales casos justifican la inmediata intervención aunque el diagnóstico sea dudoso.

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Benign Fibroma of the Pleura

Report of Case

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Primary neoplasms of the pleura are uncommon lesions. Their importance lies in the fact that the advances in the field of thoracic surgery have made their successful removal possible.

Klemperer and Rabin[1] have divided these tumors into two main groups. The first is of diffuse lesions which may involve the entire pleura and completely envelop the lung. This type of new-growth arises in the membranous lining of the pleura and has been termed an endothelioma or mesothelioma. Some pathologists now feel this is a carcinoma. It is not amenable to surgery. The second group consists of solitary or localized growths that have their origins in the sub-endothelial connective tissues on the parietal or visceral side. It is this latter group that has surgical importance.

The parietal tumors are varied in type as they may originate from any of the structures beneath the pleura. Boyd[2] has described them as the most malignant of neoplasms because they invade the chest wall early and metastasize widely. They are usually spindle-cell sarcomas, angiosarcomas, liposarcomas, and neurosarcomas. Growths arising from the visceral side are usually chondromas, lipomas, or fibromas; the last of these is the tumor with which we are here concerned.

Small fibromas are occasionally found at autopsy as pedunculated masses attached to the edges of the lung.[3] They have little clinical significance. However, some of them may grow to gigantic proportions such as the one that weighed 12 pounds which was reported by Seydel.[4] These are of interest because they may be removed surgically, and if overlooked, they may cause death through mechanical interference with vital processes. The occurrence of such a neoplasm is so unusual that we feel this case should be reported. According to Belleville[4], Unger encountered only five of these lesions in 33,000 necropsies. Belleville reviewed 44 case histories of this condition that had been recorded up to 1945.

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Report of Case

Miss E. F. (Hospital No. 180082), aged 40 years, was admitted to the Graduate Hospital on November 4, 1947, with chief complaints of shortness of breath and chest pain of two years duration. Onset of symptoms had followed a severe "cold," and they had become more marked three months prior to admission. The dyspnea was mostly evident upon exertion, and she was unable to climb a flight of stairs without distress. The chest pain occurred in two sites. There was a sharp pain over the right lower chest which was intermittent and usually disappeared during bed rest. She also described a dull ache at the xiphi-sternal junction. The ingestion of solid food occasionally was followed by a "sticking sensation" at the lower end of the sternum. An inconstant, non-productive cough had been present for one year. Prolonged attacks of coughing accentuated the pain in the right lower chest. For several months the patient had noted swelling of both ankles following a day's work. There was no history of weight loss. The past and personal histories were negative. Both parents had died of pneumonia.

Physical examination revealed an afebrile, white female in no apparent distress. The pulse rate was 80. The blood pressure was 110 mm. systolic, 70 mm. diastolic. The heart was not enlarged and no murmurs were present. The percussion note over the right lower chest was dull; this was noted below the third intercostal space anteriorly and below the inferior angle of the scapula posteriorly. The breath sounds were dim-

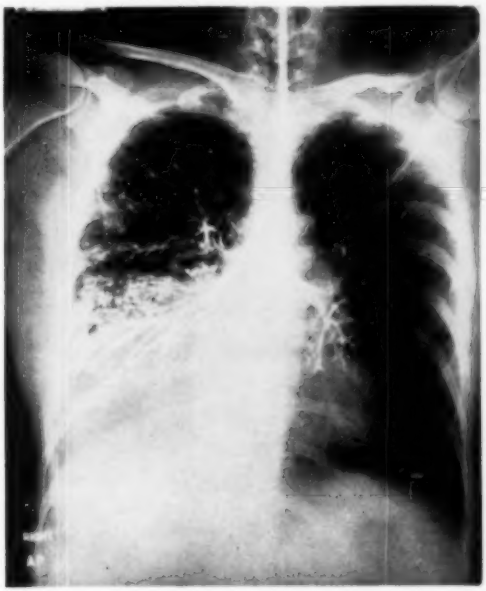

FIGURE 1: Antero-posterior bronchogram showing incomplete filling of right middle and lower lobe bronchi.

inished to absent over this area. Tactile and vocal fremitus were also diminished in this region. No rales were heard. Aside from moderate pitting edema of both legs, no other objective abnormalities were present.

Laboratory studies showed a normal blood count; hemoglobin was 72 per cent. Blood chemistry determinations were normal and the Wasserman test was negative. The electrocardiogram revealed low amplitude of the T waves.

The roentgenographic examination of the chest demonstrated a homogenous density that was obscuring the posterior portion of the right lower lung field. This radio-opacity extended up to the level of the seventh rib posteriorly. The right hemidiaphragm was not visualized. The remainder of the lung fields and the cardiovascular shadow appeared normal. Laminography gave no additional information except that rib involvement by the mass was absent. A bronchogram of the right middle and lower lobes was made by means of Lipiodol instillation (Figs. 1 and 2). Incomplete filling of the right middle and lower lobes with a crowding together and a displacement of the bronchi anteriorly and laterally was demonstrated. Although it was felt that the mass was intrathoracic in location, extension of a lesion arising in the liver could not be definitely excluded. Therefore, 400 ccm. of air were injected into the peritoneal cavity and erect films made (Fig. 3). The inferior surfaces of both hemidiaphragms were well outlined and the mass was shown to be entirely in the chest.

Endoscopic examination of the bronchi by Dr. Gabriel Tucker showed

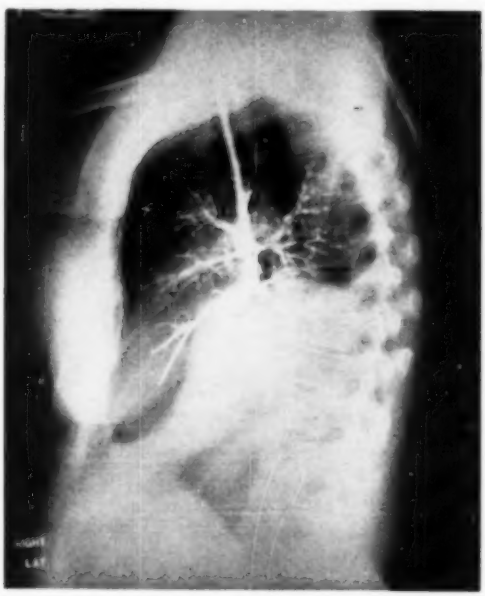

FIGURE 2: Lateral bronchogram showing smooth radio-opacity displacing bronchi.

the right main stem bronchus to be compressed. The orifice of the right middle lobe bronchus was almost obliterated. Orifices of the right lower lobe bronchi were barely seen. No inflammatory signs were noted. Papanicolau smears made of the secretions were negative for malignant cells.

Thoracotomy was performed on November 21, 1947, under endotracheal cyclopropane-ether-oxygen anaesthesia. The right seventh rib was resected and the pleural cavity entered through its bed. A large and solid tumor was visible through the incision; so the right sixth and eighth ribs were sectioned posteriorly to obtain more adequate exposure. The pleural cavity contained about 500 ccm. of turbid, orange-colored fluid and some amorphous gelatinous material. The large tumor occupied the entire right lower hemithorax and the right lower lobe was compressed into a thin crescentic shell.

A large vein and a smaller artery coursed over the antero-lateral surface of the mass and continued through a dense adhesion into the right ninth intercostal space. There was a second dense adhesive band between the inferior surface of the tumor and the diaphragm. This band measured 2 cm. in length and 1 cm. in width. These attachments were divided and the tumor was lifted upward and outward for closer inspection. It was firm and well encapsulated by visceral pleura. The outer surface was slightly nodular except over the area adjacent to the diaphragm which was flat and smooth. The mass was attached to the postero-lateral surface of the lower lobe of the right lung by a pedicle about 3 cm. in diameter. This attachment was friable and it separated from the lung paren-

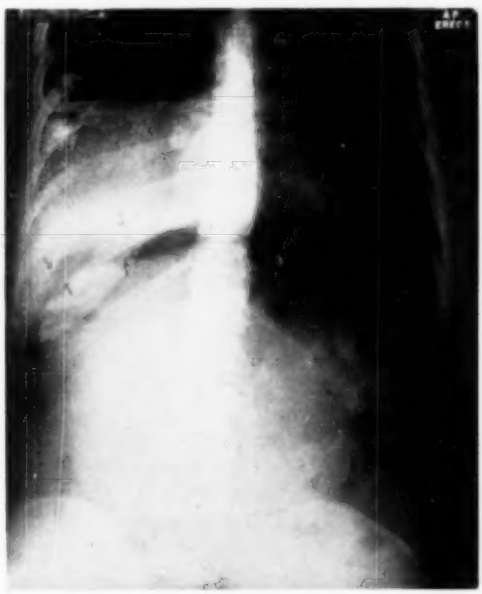

FIGURE 3: Erect film taken after artificial pneumoperitoneum. Under surface of diaphragm visualized.

chyma during mobilization of the mass. It was necessary to suture the denuded area of lung because of brisk bleeding and escape of air from the alveoli. Further exploration of the right hemithorax revealed no other lesion. The lung was expanded by the anesthetist as the chest was closed.

The tumor measured 15.5 cm. by 10.5 cm. by 7 cm. Its weight was 1500 grams. It cut with difficulty due to its dense rubbery consistency. The cut surface was pinkish white with glistening gray streaks. There were many blood-filled sinuses and cystic areas containing gelatinous material. The cut surface was irregularly elevated and depressed due to retraction of the fibrous tissue. Histologically the tumor was composed of areas of marked cellular proliferation separated by strands of dense collagen fibers (Fig. 6). The predominant cell was the fibroblast. These were spindle-shaped and were not arranged in any particular order. Palisading of the nuclei and whorl formation were not present. No mitotic figures were noted. Scattered lymphocytes and monocytes were seen. The pathological diagnosis by Dr. Eugene A. Case was Benign Fibroma of the Pleura.

The patient made an uneventful recovery. Follow-up examination 10 months after operation showed complete expansion of the right lung. She was asymptomatic and discharging her occupational duties.

Discussion

This fibroma was typical of the group; and although smaller in size, it was identical in other respects to those reported by Belleville,[4] Fawcett,[5] Boyd,[6] Mintz,[7] Lilienthal,[3] and Klemperer and Rabin.[1]

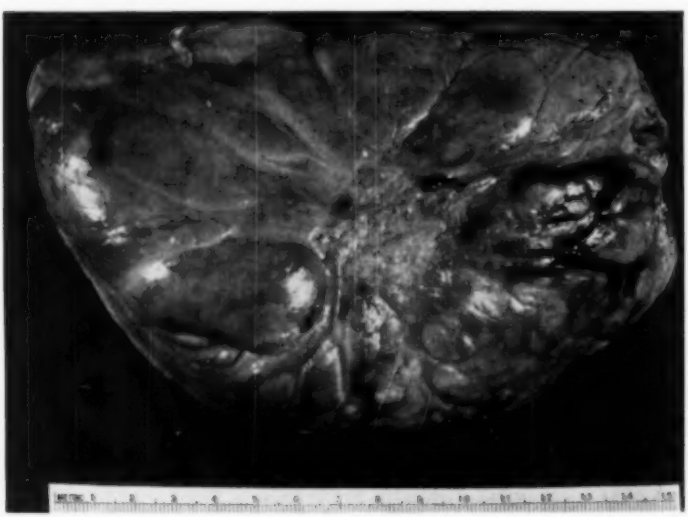

FIGURE 4: External appearance of fibroma. Area that was attached to lung is visible in center.

These tumors are observed at any age level and are slightly more common in women.[4] There is little difference in the incidence of origin in the right or left thoracic cavities.[4] There is some difference of opinion as to whether the giant fibromas arise from the parietal pleura. In most instances they are completely invested with visceral pleura and are attached to the lung by a small pedicle. It is likely that adhesions to the diaphragmatic and costal pleura form secondarily and make it difficult to determine the exact origin. On the other hand, the small pedicle and friable bands facilitate removal. This was noted in the case herein reported.

These masses are solid and irregular in shape. They are compressed to conform to the space where they are found. Lobulation may be present. The color may range from glistening white to gray. They are characterized by slow growth, and it is evident that they may attain great proportions. In one case autopsied at the Massachusetts General Hospital, a fibroma arising from the mediastinal pleura was found to occupy the entire hemithorax; Mallory estimated its weight at 20 pounds.[8]

At first these tumors were called giant sarcomas[1] because the microscopic picture was often that of a fibrosarcoma. Some were described as spindle-cell sarcomas with areas of less cellular activity resembling simple fibromas. Tumor giant cells and mitotic figures were occasionally seen. These were not noted in our case, but perhaps they were present in a section of the tumor that was

FIGURE 5: Cut surface of the tumor.

not studied. Whether classified as sarcomas or fibromas, they behave as benign lesions. Justification for this conclusion lies in the facts that they are surrounded by a connective tissue capsule, grow slowly to a great size, are not invasive, and do not metastasize. The histological picture of these tumors differs from that of the perineural fibroblastomas, because the cellular architecture of the latter is regular with palisading of the nuclei, whorl and eddy formation, and less collagen.

The symptoms and signs of the lesion are easily understood. Mechanical interference with respiration and circulation takes place as with any space-taking mass in the chest. Non-productive cough, dyspnea, chest pain, and distended neck veins may occur. Pressure on the lower esophagus may have caused the dysphagia in our case. Also the pretibial edema may have been due to interference with circulatory return. Both of these have disappeared since operation. Febrile reactions may occur secondary to pneumonitis in the compressed lung parenchyma. Pleuritic pain may be due to small hemothorax secondary to spontaneous rupture of the distended veins on the surface of the tumor. Pressure of the tumor and erosion of the ribs may also cause pain.

Roentgenography is the most important adjunct to the diagnosis of this condition. The picture is that of a uniformly dense opacity

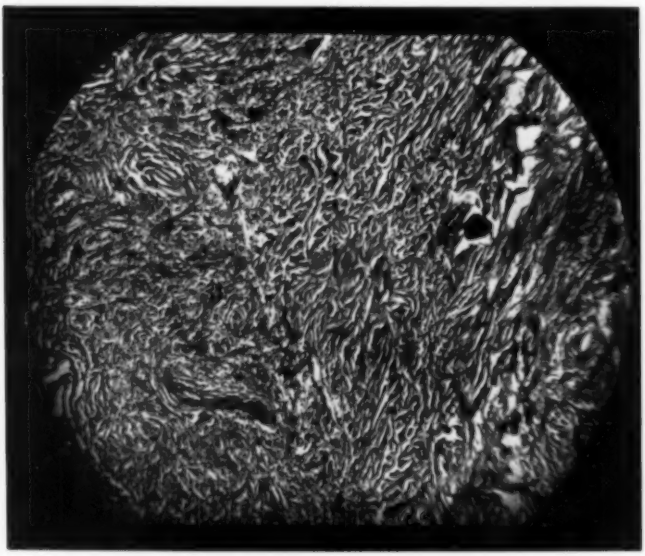

FIGURE 6: Photomicrograph of the tumor. Magnified 40X.

with a spherical contour and a sharp outline. Invasion of the hilar area is not noted. Compression of the lung tissue with little or no inflammatory change is seen. If pleural fluid is also present, the film may be interpreted as a loculated or encysted effusion, as in the case reported by Mintz.[7] If the lesion is present in the lower chest, a rhabdomyoma of the diaphragm cannot be excluded. In the case reported by Tobias, the weight of the mass had caused an inversion of the diaphragm, and the lesion appeared to be intra-abdominal.[4] Artificial pneumothorax or pneumoperitoneum may be of great value in defining the limits of the tumor. This was borne out by our case, because of neoplasm of the liver could not be ruled out until the upper surface of the liver was defined by air.

Bronchoscopic examination is necessary to differentiate this condition from one of intra-bronchial origin.

The only therapy is surgical intervention with complete removal of the fibroma. The prognosis is good. Recurrence has been reported after partial excision of these tumors.[3]

SUMMARY

1) Primary neoplasms of the pleura may be divided into two main groups: one of diffuse lesions involving the entire pleura; and one of solitary, localized growths originating in the subendothelial connective tissues on the parietal or visceral side. The latter tumors are as varied as the tissues from which they originate.

2) Large benign fibromas of the pleura are rare; only 44 had been recorded up to 1945.

3) A case of benign fibroma of the pleura is reported. This tumor was resected, and the patient made an uneventful recovery. The mass weighed 1500 grams.

4) The symptoms and signs of these tumors are those of a space-taking lesion in the thorax. Mechanical interference with respiration and circulation occur.

5) Some have called these tumors giant sarcomas, but they usually behave as benign lesions. They appear to grow slowly to great size, do not invade adjacent tissues, and do not metastasize.

6) Roentgenography of the chest is most important in the diagnosis of these lesions. Bronchoscopy is also of value. The importance of artificial pneumothorax or pneumoperitoneum and subsequent roentgenography in ruling out intra-abdominal pathology is discussed.

7) Good results are obtained with complete removal of the fibroma. Recurrence has been reported after partial excision.

RESUMEN

1) Las neoplasmas benignos de la pleura pueden dividirse en dos grupos principales; uno de lesiones difusas que abarcan toda la pleura y el otro de neoformaciones solitarias localizadas a partir del tejido subendotelial conectivo en el lado parietal o en el visceral. Estos últimos tumores son tan diversos como son los tejidos de que originan.

2) Los fibromas benignos grandes de la pleura son raros; solo 44 se han referido hasta 1945.

3) Se relata un caso de fibroma benigno de la pleura. Este tumor fué resecado y el enfermo se recuperó sin incidentes. El tumor pesaba 1500 gramos.

4) Los síntomas y los signos de estos tumores son los de los padecimientos que invaden el espacio de la caja torácica. Hay interferencia mecánica con la respiración y la circulación.

5) Algunos han llamado a estos tumores sarcomas gigantes, pero se conducen como tumores benignos. Parece que crecen lentamente hasta llegar a gran tamaño, no invaden los tejidos vecinos y se metastatizan.

6) Para el diagnóstico de estos tumores la radiografía es lo más importante. La broncoscopía es también de valor. Se discute la importancia del neumotórax y del neumoperitoneo para diferenciar de las neoformaciones intrabdominales.

7) Se obtienen buenos resultados con la completa extirpación del fibroma. Después de resección parcial se han referido recurrencias.

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6 Boyd, William: "Surgical Pathology," *W. B. Saunders Co.*, Philadelphia, 1947.
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Sixteenth Annual Meeting

American College of Chest Physicians

ST. FRANCIS HOTEL,
San Francisco, California

JUNE 22-25, 1950

Preliminary Program

THURSDAY, JUNE 22:

9:00 a. m. ***Oral Examinations***

2:00 p. m. ***Written Examinations***
Candidates are requested to report to the Board of Examiners at 8:30 a. m.

10:00 a. m. ***Annual Meeting, Board of Governors***

2:00 p. m. ***Annual Meeting, Board of Regents***

12:00 noon ***Luncheon Meeting***
Annual Conference of College Chapter Officials
Board of Regents
Board of Governors

Awarding of Certificates of Merit to Past-Presidents of College Chapters
Joseph C. Placak, M.D., President, presiding

8:00 p. m. ***Council on International Affairs***

Council on Pan American Affairs
Richard H. Overholt, Brookline, Massachusetts

Council on European Affairs
Andrew L. Banyai, Milwaukee, Wisconsin

Council on Pan Pacific Affairs
Seymour M. Farber, San Francisco, California

Council on African and Eastern Affairs
Edgar Mayer, New York, New York

"Streptomycin in the Treatment of Tuberculosis,"
Manuel Albertal, Buenos Aires, Argentina

"Observations on Paragonomiasis at the Quezon Institute,"
Miguel Canizares, Manila, Philippine Islands

"The Endoscopic Approach to the Autonomic Nervous System and Its Therapeutic Possibilities,"
E. F. Kux, Innsbruck, Austria

Guest Speaker: Manoel de Abreu, Rio de Janeiro, Brazil
Reports of Council Chairmen

All Councils and Committees will meet on Thursday, June 22nd.

FRIDAY, JUNE 23:

9:00 a. m. ***Scientific Session***

"The Comparative Morphology of Acid Fast Bacilli,"
Emil Bogen, Olive View, California
Discussion by Henry C. Sweany, Chicago, Illinois

"Streptomycin and Artificial Pneumoperitoneum in Pulmonary Tuberculosis,"
Benjamin L. Brock, Downey, Illinois
Discussion by Andrew L. Banyai, Milwaukee, Wisconsin

"Clinical Results and Physiologic Effects of Immobilizing Lung Chamber Therapy in Patients with Pulmonary Tuberculosis,"
Alvan L. Barach, New York, New York
Discussion by G. L. Bellis, Winnebago, Wisconsin

"Complications Following Pulmonary Resection for Tuberculosis in Streptomycin Treated Patients,"
James B. Murphy, Harry E. Walkup, Hawley H. Seiler and S. Bornstein, Oteen, North Carolina
Discussion by W. L. Rogers, San Francisco, California

"Pulmonary Resection for Tuberculosis,"
Richard H. Overholt, Norman J. Wilson and Francis M. Woods, Brookline, Massachusetts
Discussion by John B. Grow, Denver, Colorado

2:00 p. m. ***Scientific Session:***

"The Use of Antibiotics in the Treatment of Pulmonary Emphysema."
Edwin R. Levine, Chicago, Illinois
Discussion by Burgess Gordon, Philadelphia, Pennsylvania

"Pulmonary Mycotic Disease: Differential Diagnosis."
Arthur W. Duryea, Alexandria, Louisiana

X-Ray Seminar conducted by Leo G. Rigler, Minneapolis, Minnesota

8:00 p. m. ***Motion Picture Session:***
Paul H. Holinger, Chicago, Illinois, Chairman

SATURDAY, JUNE 24:

9:00 a. m. ***Administrative Session:***
Joseph C. Placak, President, presiding

Report of the Treasurer
Benjamin L. Brock, Downey, Illinois

Report of the Committee on Nominations
Robinson O. Joplin, Louisville, Kentucky

Report of the Executive Secretary
Murray Kornfeld, Chicago, Illinois

Report of the Committee on Board Certification
J. Winthrop Peabody, Washington, D. C.

Report on Standards for Tuberculosis Hospitals and Sanatoria as approved by the American College of Surgeons and the Council of Tuberculosis Hospitals and Committee on Sanatorium Standards of the American College of Chest Physicians

Malcolm T. MacEachern, Director Emeritus, In Charge of Hospital Activities, American College of Surgeons, Chicago, Illinois

R. S. Anderson, Chairman, Council of Tuberculosis Hospitals, American College of Chest Physicians, Erie, Pennsylvania

I. D. Bobrowitz, Chairman, Committee on Sanatorium Standards, American College of Chest Physicians, Otisville, New York

Report of the Council on the Management and Treatment of Diseases of the Chest
Edwin R. Levine, Chicago, Illinois

Report of the Committee on Chemotherapy and Antibiotics
Karl H. Pfuetze, Cannon Falls, Minnesota

Report of the Committee on Non-Surgical Collapse Therapy
Harold G. Trimble, Oakland, California

Report of the Council on Research
Charles M. Hendricks, El Paso, Texas, General Chairman

Report of the Financial Section
Jay Arthur Myers, Minneapolis, Minnesota, Chairman

Report of the Scientific Section
Alvan L. Barach, New York, New York, Chairman

10:30 a. m. ***Scientific Session:***

"Bronchial Lavage,"
Manoel de Abreu, Rio de Janeiro, Brazil
Discussion by Harold G. Trimble, Oakland, California

"The Role of Bronchoscopy in the Diagnosis and Treatment of Bronchial Adenoma,"
Chevalier L. Jackson, Philadelphia, Pennsylvania
Discussion by Paul H. Holinger, Chicago, Illinois

2:00 p. m. ***Scientific Session:***

"Clinical Evaluation of Cytologic Studies in the Diagnosis of Carcinoma of the Lung,"
Seymour M. Farber, San Francisco, California
Discussion by Alton Ochsner, New Orleans, Louisiana

"Reversible Forms of Heart Disease,"
John F. Briggs, St. Paul, Minnesota
Discussion by Arlie R. Barnes, Rochester, Minnesota

"Cardio-Respiratory Studies in Pre and Post Operative Funnel Chest (Pectus Excavatum),"
A. Lincoln Brown, San Francisco, California
Discussion by Fred R. Harper, Denver, Colorado

"Resection of the Auricular Appendage,"
William D. Longmire, Jr., Los Angeles, California

6:00 p. m. ***Annual Convocation:***
Joseph C. Placak, President, presiding

Awarding of Fellowship Certificates
James H. Stygall, Indianapolis, Indiana,
Chairman, Board of Regents

Report of the Historian
William A. Hudson, Detroit, Michigan

Guest Speaker: Paul C. Smith, Editor and General Manager, San Francisco Chronicle

6:30 p. m. ***Social Hour***

7:00 p. m. ***Presidents' Banquet:***

Toastmaster
William C. Voorsanger, San Francisco, California

Introduction of Guests from Other Countries

President's Address
Joseph C. Placak, Cleveland, Ohio

Introduction of President-Elect
Louis Mark, Columbus, Ohio

Presentation of College Medal
Jay Arthur Myers, Minneapolis, Minnesota, Chairman

SUNDAY, JUNE 25:

9:00 a. m. ***Scientific Session:***

"Tuberculosis Control in Institutions for the Mentally Ill."
Edmund W. Miller, Anoka, Minnesota
Discussion by Jay Arthur Myers, Minneapolis, Minnesota

"Bronchogenic Carcinoma Masquerading as Other Diseases of the Chest,"
J. Karl Poppe, Portland, Oregon
Discussion by Ephraim Korol, Downey, Illinois

"Surgical Treatment of Various Circumscribed (Coin) Intrathoracic Lesions,"
S. W. Harrington, Rochester, Minnesota
Discussion by Paul C. Samson, Oakland, California

"The PAS Salt of Streptomycin,"
Edward Dunner, Livermore, California
Discussion by William S. Klein, Spivak, Colorado

"The Present Status of Antibiotic Treatment of Pulmonary Tuberculosis."
H. Corwin Hinshaw, San Francisco, California
Discussion by John Barnwell, Washington, D. C.

2:00 p. m. ***Scientific Session:***

"Considerations of the Clinical Physiologic Factors in the Treatment of Chronic Pulmonary Conditions,"
Burgess Gordon, Philadelphia, Pennsylvania

"Oleothorax Following Pulmonary Resection,"
Neil C. Andrews, Douglas R. Morton, George M. Curtis and Karl P. Klassen, Columbus, Ohio

"Indications and Contra-Indications for Use of Decortication Procedures in Tuberculous Patients,"
Osler A. Abbott, Atlanta, Georgia

"Extrapleural Pulmonary Resection: The Importance of the Pleura (Study of 150 Consecutive Operations),"
I. G. Tchertkoff and I. J. Selikoff, New York, New York

5:00 p. m. ***Meeting, Board of Regents***

Round Table Luncheons

FRIDAY, JUNE 23:

A-1 "Bronchial Asthma,"
Albert H. Andrews and Leon Unger, Chicago, Illinois

A-2 "Management of Tuberculosis in the Older Age Group."
A. Worth Hobby, Atlanta, Georgia and Foster Murray, Brooklyn, New York

A-3 "Suppurative Diseases of the Lung."
Coleman Rabin, New York, New York and
Fred R. Harper, Denver, Colorado

A-4 "BCG Vaccination."
Jay Arthur Myers, Minneapolis, Minnesota, Sol Roy Rosenthal, Chicago, Illinois, Sidney J. Shipman, San Francisco, California and Robert J. Anderson, Washington, D. C.

A-5 "Evaluation of Pulmonary Function."
George G. Ornstein, New York, New York

A-6 "Air Contamination."
Robert A. Kehoe, Cincinnati, Ohio

SATURDAY, JUNE 24:

B-1 "Management of Cavitary Tuberculosis in Young People."
David Ulmar, New York, New York, Donato G. Alarcon, Mexico City, Mexico and John B. Grow, Denver, Colorado

B-2 "Dust Diseases."
Oscar Sander, Milwaukee, Wisconsin

B-3 "Use and Dosage of Newer Antibiotics and Chemicals in Tuberculosis."
Karl Pfuetze, Cannon Falls, Minnesota, Emil Bogen, Olive View, California, Arnold Shamaskin, Hines, Illinois and
H. Corwin Hinshaw, San Francisco, California

B-4 "Home Management of Tuberculosis."
Clarence Payne, Chicago, Illinois and
Eli H. Rubin, New York, New York

B-5 "Pneumoperitoneum."
Andrew L. Banyai, Milwaukee, Wisconsin and
Harold G. Trimble, Oakland, California

B-6 "The Value of Antihistamines in the Common Cold."
Frank R. Ferlaino, New York, New York, Fred W. Wittich, Minneapolis, Minnesota and H. E. Tebrock, New York, New York

SUNDAY, JUNE 25:

C-1 "Fungus Diseases of the Chest."
Charles E. Smith, Berkeley, California, Alvis E. Greer, Houston, Texas and Michael L. Furcolow, Kansas City, Kansas

C-2 "Emphysema."
Alvan L. Barach, New York, New York

C-3 "When Should Pneumothorax be Terminated."
Louis Mark, Columbus, Ohio and
Edward W. Hayes, Monrovia, California

C-4 "Bronchiectasis and Bronchitis."
Paul C. Samson, San Francisco, California and
Louis L. Friedman, Birmingham, Alabama

C-5 "Use and Dosage of Newer Antibiotics in Nontuberculous Diseases."
Wallace E. Herrell, Rochester, Minnesota

C-6 "Evaluation of the Cardiac Status of Patients."
Italo Volini, Chicago, Illinois

Dr. Manoel de Abreu

Dr. Manoel de Abreu, Professor of Radiology, Faculty of Medical Sciences, Rio de Janeiro, Brazil, will be a guest speaker at the Sixteenth Annual Meeting of the American College of Chest Physicians to be held in San Francisco. Dr. de Abreu is noted for developing the 35 mm. photofluorographic x-ray equipment. His work has made possible low cost mass chest x-ray surveys. Dr. de Abreu also did the original work on bronchial lavage and will discuss this subject at the San Francisco meeting.

Other guest speakers on the program will be Dr. Miguel Canizares of the Philippine Islands, Regent of the College for the Philippines, Dr. Manuel Albertal of Buenos Aires, Argentina, a member of the Committee on Chemotherapy and Antibiotics of the College, and Dr. E. F. Kux of Innsbruck, Austria.

COMMITTEE ON NOMINATIONS

Recommendations for nominations to elective offices in the College expiring June, 1950 should be addressed to Dr. R. O. Joplin, Brown Building, Louisville, Kentucky, Chairman of the Committee on Nominations. The other members of the Committee on Nominations are Dr. David W. Heusinkveld, Cincinnati, Ohio and Dr. James H. Stygall, Indianapolis, Indiana.

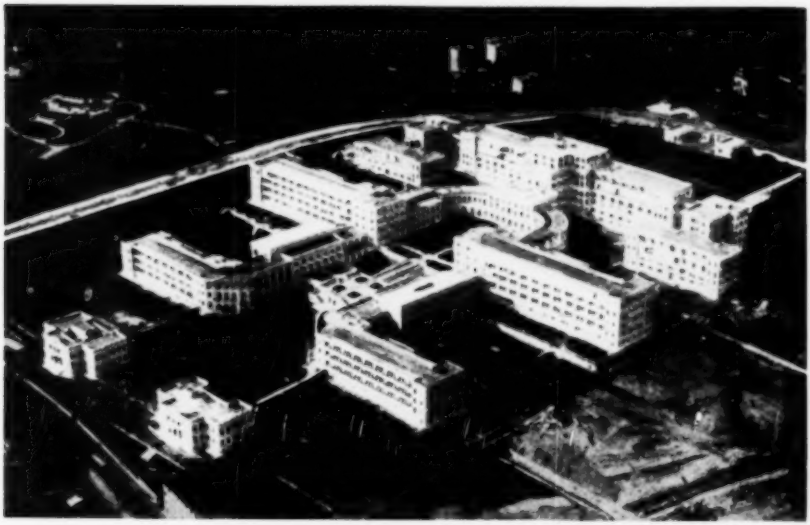
NEW OFFICERS OF THE COLLEGE

Chevalier L. Jackson, Philadelphia, Pennsylvania, First Vice-President (to complete the unexpired term of Harry C. Warren, San Francisco, California, deceased July 29, 1949).

Andrew L. Banyai, Milwaukee, Wisconsin, Second Vice-President (to complete the unexpired term of Chevalier L. Jackson).

James H. Stygall, Indianapolis, Indiana, Chairman, Board of Regents (to complete the unexpired term of Paul A. Turner, Louisville, Kentucky, deceased April 13, 1950).

First International Congress on Diseases of the Chest



Carlo Forlanini Institute, Rome Italy

SEPTEMBER 17 - 22, 1950

One hundred subjects will be presented by more than 100 speakers at the First International Congress on Diseases of the Chest to be held in Rome, Italy, September 17-22, 1950.

Because of the unprecedented demand for places on the program, the committee on arrangements has found it necessary to extend the Congress an additional two days. It is suggested that physicians who plan to attend the Congress arrange their itineraries accordingly.

Preliminary Program

"Evaluation of Conservative and Radical Surgical Procedures in Pulmonary Tuberculosis,"
Donato G. Alarcon, Mexico City, Mexico

"Streptomycin in the Treatment of Tuberculosis,"
Manuel Albertal, Buenos Aires, Argentina

"Major Thoracic Surgery in Pulmonary Tuberculosis,"
Armando Alonso Vial, Santiago, Chile

"Community-Wide Case-Finding by Chest X-ray Examination,"
Robert J. Anderson, Washington, D. C., U.S.A.

"Simultaneous Bilateral Artificial Pneumothorax,"
Maurizio Ascoli, Palermo, Italy

"Surgical Management of Cavitary Tuberculosis,"
G. Babolini, Naples, Italy

"Pulmonary Problems of Schistosomiasis in Men,"
Jose Ignacio Baldo, Caracas, Venezuela

"The Clinical Application of Artificial Pneumoperitoneum,"
Andrew L. Banyai, Milwaukee, Wisconsin, U.S.A.

"Anatomico-Clinical Forms of Bronchogenic Carcinoma,"
M. Bariety and J. Paillas, Paris, France

"Nontuberculous Spontaneous Pneumothorax and Its Treatment,"
Etienne Bernard and Andre Meyer, Paris, France

"Use and Value of Angiopneumography,"
P. Bourgeois and Vic-Dupont, Paris, France

"Pulmonary Mimicry in Bronchogenic Carcinoma,"
John F. Briggs, St. Paul, Minnesota, U.S.A.

"Congenital Deformities of the Anterior Chest Wall,"
Henry A. Brodkin, Newark, New Jersey, U.S.A.

"Observations on Paragonomiasis at the Quezon Institute,"
Miguel Canizares and Jose Celis, Quezon City, Philippine Islands

"Laryngeal-Tracheo-Bronchial Anesthesia with Sub-posological Doses of Pontocaine in Bronchoscopy and Bronchography,"
A. Albert Carabelli, Trenton, New Jersey, U.S.A.

"Antibiotic Therapy and Artificial Pneumothorax,"
R. Unberto Carpi, Milan, Italy

"Aspergillosis of the Lung,"
Panyotis Chortis, Athens, Greece

"Functional Studies on the Mediastinum,"
L. Condorelli, Rome, Italy

"Phthisiogenesis and the Tuberculin Reaction,"
Gennero Costantini, Bologna, Italy

"Domiciliary Treatment in the Battle Against Tuberculosis in Crowded Cities,"
J. Wallace Craig, London, England

"Bronchial Lavage in Diagnosis,"
Manoel de Abreu, Rio de Janeiro, Brazil

"The Effect of PAS in Tuberculosis from Clinical, Anatomico-Pathological and Experimental Viewpoints,"
G. Daddi, C. Pana, Giusto Fegiz and C. Cattaneo, Rome, Italy

"Histologic Development of Early Tuberculosis and Its Alteration by Streptomycin,"
Jacques Delarue, Paris, France

"Medico-Legal Aspects of Silicosis,"
M. R. Even, Paris, France

"Cytologic Diagnosis of Lung Cancer,"
Seymour M. Farber, San Francisco, California, U.S.A.

"Industrial Pulmonary Dust Diseases and Control of Hazards,"
Frank R. Ferlaino, New York, New York, U.S.A.

"Constitutional Factors in the Pathogenesis of Tuberculosis,"
Vincenzo Fici, Palermo, Italy

"Primary Atypical Pulmonitis,"
C. Frugoni, et al, Rome, Italy

"Emphysematous Bullae and Pneumatoceles: Anatomico-Clinical Differentiation,"
Pierre M. Galy, Lyon, France

"The Catheterization of the Right Cavities of the Heart and of the Exploration of Cardio-Respiratory Functions in Experimental Animals,"
Victor Gimenez, Angel Larralde and J. Delgado Blanco, Caracas, Venezuela

"Bronchotomy for Bronchial Adenoma,"
Alfred Goldman, Beverly Hills, California, U.S.A.

"Collapse Therapy in Ambulatory Tuberculous Patients,"
R. Heller, Hounslow, Middlesex, England

"Obscure Pulmonary Bleeding,"
J. J. Hennessey, Hartford, Connecticut, U.S.A.

"Tumors of the Esophagus,"
William A. Hudson, Detroit, Michigan, U.S.A.

"Carcinoma of the Lung and Chromates,"
Stelio Imprescia, Perry Point, Maryland, U.S.A.

"Adenoma of the Bronchus,"
Chevalier L. Jackson, Philadelphia, Pennsylvania, U.S.A.

"Apicopexy in Semb's Thoracoplasty,"
Nicholas Jannopoulos, Athens, Greece

"Vaccination with BCG in the Mexican Republic,"
Miguel Jimenez, Mexico City, Mexico

"The Twilight of Artificial Pneumothorax,"
R. Y. Keers, Aberdeenshire, Scotland

"General Principles and Results of Treatment of Pulmonary Suppurations,"
R. Kourilsky, M. Mathey, Regaud and P. Daumet, Paris, France

"The Endoscopic Approach to the Autonomic Nervous System and Its Therapeutic Possibilities (Especially in Duodenal Ulcer, Hypertension, Angina Pectoris and Diabetes Mellitus),"
E. F. Kux, Innsbruck, Austria

"Incidence of Chest Diseases in Various Countries,"
Giovanni L'Eltore, Rome, Italy

"The Pulmonary Circulation Under Different Pathological Conditions,"
Lopo de Carvalho, Lisbon, Portugal

"The Status of Extrapleural Pneumothorax,"
H. Martinez de Alva, Tijuana, Mexico

"Chemotherapeutic Tamponade of Lung Cavities,"
Gustav Maurer, Davos, Switzerland

"Pulmonary Fibrosis,"
Edgar Mayer, New York, New York, U.S.A.

"Biological Dynamics of Tuberculosis,"
V. Monaldi, Naples, Italy

"Observations on Extrapleural Pneumothorax: Report on 1,100 Cases,"
O. Monod, Paris, France

"Apico-Axillary and Basal Extrapleural Pneumothorax,"
Eugenio Morelli, Rome, Italy

"Decortication and Lung Resection in Pulmonary Tuberculosis,"
Papken S. Mugrditchian, Beirut, Lebanon

"Primary Tuberculosis in Adults,"
Jay Arthur Myers, Minneapolis, Minnesota, U.S.A.

"Open and Closed Extrapleural Technique,"
Andre Marmet, Colmar, France

"Bronchiectasis in Childhood and Adult Pulmonary Tuberculosis,"
Antonio Navarrete and Teodosio Valledor, Havana, Cuba

"Tuberculosis as General Infection,"
N. B. Oekonomopoulos, Athens, Greece

"Our Therapeutic Experience with Antibiotics in Pulmonary Tuberculosis,"
H. Orrego Puelma, Santiago, Chile

"The Benefits of Excision in Lung Disease,"
Richard H. Overholt, Brookline, Massachusetts, U.S.A.

"Tumors of the Mediastinum,"
R. Paolucci, Rome, Italy

"Contribution to the Problem of International Classification of Pulmonary Tuberculosis with Code,"
Basil Papanikolaou, Athens, Greece

"Pneumonectomy and Total Pleurectomy for Uncontrolled Pulmonary Tuberculosis and Empyema,"
Juda M. Pauzner, Petach Tikva, Israel

"Physiotherapy in Nonsurgical Pulmonary Disease,"
Alan H. Penington, Melbourne, Australia

"Treatment of Intestinal Tuberculosis with Antibiotics and Chemotherapy,"
F. Piechaud and P. Freour, Bordeaux, France

"Changing Concepts of the Indications for Collapse Therapy in Pulmonary Tuberculosis,"
Benjamin P. Potter, Jersey City, New Jersey, U.S.A.

"Streptomycin Therapy in Tuberculosis: Prevention of Streptomycin Resistance by Adequate Collapse Therapy,"
Albert J. J. Reginster, Liege, Belgium

"The Collapse Phenomenon of the Great Veins of the Thorax (Angiocardiographic Studies),"
Ricardo, Rimini, Montevideo, Uruguay

"Neurogenic Tumors of the Mediastinum,"
Cesar Rodriguez, Victor Brito and Leandro Potenza, Caracas, Venezuela

"Heart Surgery,"
A. Rodriguez Diaz, Havana, Cuba

"Medical Treatment of Lung Abscess,"
Tevfik Saglam, Istanbul, Turkey

"Pulmonary Manifestations of Schistosomiasis,"
Abdel-Aziz Sami, Cairo, Egypt

"Extrapleural Pneumothorax: Indications and Results Based on the Analysis of 1,500 Cases,"
Marcel B. Santy, Lyon, France

Title to be announced,
Luis Saye, Buenos Aires, Argentina

"The Protective Power of BCG in Allergics,"
Jose Silveira, Salvador, Bahia, Brazil

"Contributions to the Clinical Study of Cystic Diseases of the Lung,"
Raul Soules-Baldo, Caracas, Venezuela

"Physio-Pathology of the Middle Lobe,"
A. Soulas and J. M. Lemoine, Paris and
P. Mounier-Kuhn, Lyon, France

"Treatment of Tuberculous Meningitis and Miliary Tuberculosis with Emphasis on Prolonged Streptomycin Therapy,"
Moses J. Stone, Boston, Massachusetts, U.S.A.

"Further Studies on PAS in the Treatment of Pulmonary Tuberculosis,"
Henry C. Sweany, Chicago, Illinois, U.S.A.

"The Surgical Rehabilitation of the Coronary Cripple,"
Samuel A. Thompson, New York, New York, U.S.A.

"Coccidioidomycosis,"
Harold G. Trimble, Oakland, California, U.S.A.

"Small Thoracoplasties,"
Alexander Tuxen, Asker, Norway

"Experience with TB-I in the Treatment of Tuberculosis,"
Alvaro Urgoiti, La Coruna, Spain

"Echinococcus Cysts of the Chest,"
S. Valdoni, Rome, Italy

"Tropical Eosinophilosis,"
Raman Viswanathan, New Delhi, India

"Neomycin—Experimental and Clinical Studies,"
Italo F. Volini, Chicago, Illinois, U.S.A.

"Use of Streptomycin by Endocavitary Application and in the Surgical Treatment of Pulmonary Tuberculosis,"
A. Omodei Zorini and G. Bottari, Rome, Italy

Clinical-Pathological Conference, Wednesday, September 20th

A Clinical-Pathological Conference will be presented in the surgical and x-ray departments of the Forlanini Institute on Wednesday afternoon, September 20. The following physicians will give demonstrations at the Conference: A. Omodei Zorini, L. Pigorini, G. Bottari, N. Di Paola, G. Zorzoli, N. Montanini, C. Pana, U. Canova, G. De Maria, S. Maccagni, Pensa, C. Cattaneo, P. Morellini, G. Daddi and Mariani.

ACTIVITIES PLANNED DURING CONGRESS

Delegates to the Congress will have been notified by letter from the Italian Secretary Office of the Congress the address of the hotel where reservations have been made for them. Members of the Committee on Housing will be available at the railway station for delegates without hotel accommodations. All delegates will have been notified by letter the telephone number of the Secretary Office where they may apply for information. The delegates will find at their respective hotels, envelopes containing the program for the Congress, badge, announcements, etc.

SUNDAY, SEPTEMBER 17:

The Inaugural Ceremony to open the Congress will be held in the morning at the "Orazi e Curiazi" Hall in the Capitol building. The Town Mayor will welcome the delegates in the presence of other Italian and foreign authorities after which deputies for the Italian Government, the High Commissariat for Hygiene and Health, the Institute of Social Providence, and the Italian Federation for the Fight against Tuberculosis will greet the delegates. Brief addresses will be made by Professor Eugenio Morelli and Professor A. Omodei Zorini, the Co-Chairmen of the Congress. Officers of the American College of Chest Physicians will then be introduced and the Congress will officially be declared open. Fellowship Certificates will be awarded to new Fellows of the College and to the Honorary Members of the Italian Federation for the Fight against Tuberculosis. Refreshments will follow.

MONDAY, SEPTEMBER 18:

A tour of the Carlo Forlanini Institute will take place between 8:30 and 10:30 in the morning and at 10:30 the scientific sessions will open. A tour of Rome is scheduled for the evening.

TUESDAY, SEPTEMBER 19:

The scientific sessions at the Carlo Forlanini Institute will be held in the morning and afternoon as on the previous day. In the evening arrangements have been made for the delegates to attend a concert.

WEDNESDAY, SEPTEMBER 20:

The scientific sessions will be held in the morning and afternoon as on the previous days. In the afternoon there will also be a clinical-pathological conference. Dinner in a characteristic Roman restaurant has been scheduled for the evening.

THURSDAY, SEPTEMBER 21:

There will be scientific sessions in the morning and the scientific assembly will officially close at noon. In the afternoon there will be excursions by motor bus to Tivoli to visit the Villa d'Este, a visit to the University Town and to the High Institute of Health. There will be a formal banquet in the evening.

FRIDAY, SEPTEMBER 22:

Delegates will be received by the Pope on Friday morning and a tour of the Vatican City will follow. In the afternoon it is tentatively planned to visit either Naples or Sondalo.

The Ladies Committee on Entertainment is arranging a program of receptions and visits to various interesting places to entertain the doctors' wives.

College Chapter News

ARIZONA CHAPTER

The Arizona Chapter held its annual meeting in conjunction with the chest section of the Arizona State Medical Society at the Westward Ho Hotel, Phoenix, on May 1. The meeting opened with a luncheon followed by the scientific program as given below:

"Surgery of Congenital Heart Disease,"
Howard T. Barkley, M.D., F.C.C.P., Houston, Texas

"Discussion with Emphasis on Diagnostic Problems,"
George C. Griffith, M.D., Los Angeles, California

"Pulmonary Calcification,"
Michael L. Furcolow, M.D., Kansas City, Kansas

"Exploratory Thoracotomy as a Diagnostic Procedure,"
Howard T. Barkley, M.D., F.C.C.P., Houston, Texas

ILLINOIS CHAPTER

The Illinois Chapter of the College will hold its annual meeting at the Abraham Lincoln Hotel, Springfield, on Tuesday evening, May 23, at the time of the annual meeting of the Illinois State Medical Society, May 23-25. The following program has been planned:

5:00 p. m. Business Meeting and Election of Officers

6:30 p. m. Dinner Meeting

Guest Speakers:

"Use of Streptomycin and Other Antibiotics in the Treatment of Tuberculosis,"
David T. Carr, M.D., Rochester, Minnesota

"Primary Atypical Pneumonia: General Therapy and Evaluation of the Newer Antibiotics,"
Italo F. Volini, M.D., F.C.C.P., Chicago, Illinois

MINNESOTA CHAPTER

The Minnesota Chapter of the College has arranged the following program to be presented in the section on diseases of the chest in the Minnesota State Medical Association on June 12, at the Armory in Duluth:

"Surgery of Valvular Heart Disease,"
Ivan Baronofsky, M.D., Minneapolis

"Ciliary Action and the Mechanism of Atelectasis,"
Anderson Hilding, M.D., Duluth

"Significance of Isolated Nodules in the Lung (Follow-up Report in Collaboration with Thomas Kinsella, M.D., F.C.C.P., Minneapolis)," David Sharp, M.D., F.C.C.P., Minneapolis

"Clinical Evaluation of Pulmonary Insufficiency,"
Philip Soucheray, M.D., Minneapolis

"Perforations of the Esophagus,"
William Seybold, M.D., Rochester

The program committee for this meeting consists of Drs. B. J. Terrell, Nopeming, D. W. Wheeler, Duluth and Roy Mayne, Nopeming.

CUBAN CHAPTER MEETING

Photograph taken at the luncheon meeting of the officers of the Cuban Chapter held in Havana, on January 18. Reading left to right: Dr. Teodosio Valledor; Dr. Gustavo Aldereguia; Dr. Carlos F. Barroso, Secretary-Treasurer; Dr. Elva Perez-Medina; Dr. Octavio Rivero, Governor; Dr. Antonio Navarrete, Regent; Mr. Murray Kornfeld; Dr. Francisco J. Menendez, President; Dr. Rene Garcia Mendoza; Dr. Ricardo Sanchez Acosta, Vice-President; and Dr. Alfredo Antonetti.

CUBAN CHAPTER

The officers of the Cuban Chapter of the College held a luncheon meeting in Havana on Saturday, January 18, at the time of the visit to Havana by Mr. Murray Kornfeld, Chicago, Executive Secretary of the American College of Chest Physicians. Announcement of the First International Congress on Diseases of the Chest to be held in Rome, Italy next September, was made by Mr. Kornfeld. Dr. Antonio Navarrete, Regent of the College for Cuba, accompanied by Mr. Kornfeld, subsequently paid a visit to the Minister of Health of Cuba to arrange for the cooperation of the Cuban Government in appointing official delegates to the International Congress.

The Cuban Chapter will celebrate its Tenth Anniversary in 1950 and plans for the anniversary meeting to be held in Havana next December were also discussed at the luncheon meeting. Dr. Francisco J. Menendez, President of the Chapter, presided at the meeting and gave a brief talk about the various activities of the chapter. Dr. Menendez reported that the membership of the College in Cuba has increased from 26 in December, 1948, to 43 members as of January, 1950, an increase of 65 per cent. A number of additional applications for membership are pending.

A one week postgraduate course in diseases of the chest is being arranged for presentation this year by the Cuban Chapter. The course will be given wide publicity in Cuba and the West Indies.

NEW ENGLAND STATES CHAPTER

The New England States Chapter of the College will hold a meeting at the Deaconess Hospital, Boston, Massachusetts on Wednesday, May 10. Dr. Richard H. Overholt and Dr. Leo Kenney of Boston will talk on the subject of "Costoversion One-Stage Thoracoplasty." A business meeting will follow.

NEW JERSEY CHAPTER

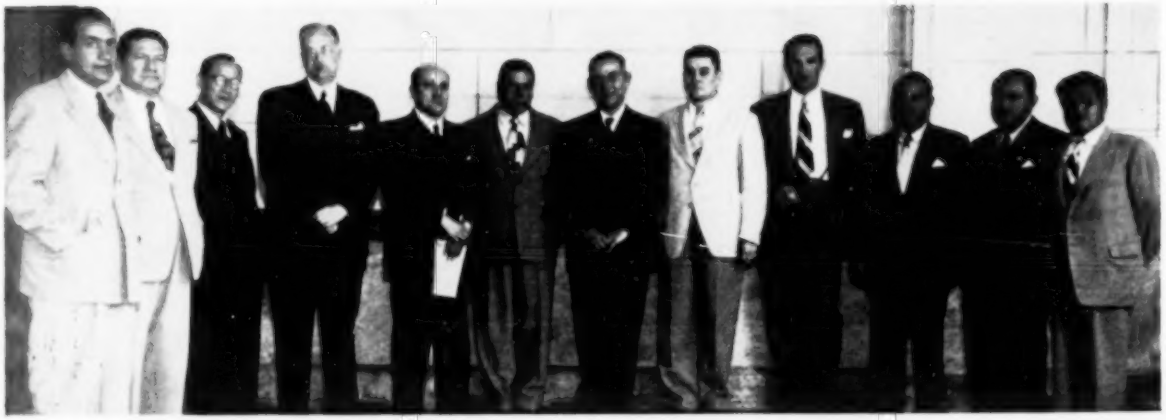
The annual meeting of the Section on Diseases of the Chest of the Medical Society of New Jersey, will be held at the Haddon Hall Hotel, Atlantic City, on Wednesday, May 24. The members of the New Jersey Chapter will participate in the meeting. The following program will be presented:

"Extrapleural Pulmonary Resection: Evaluation of New Procedure,"
Irving J. Selikoff, M.D., F.C.C.P., Paterson, New Jersey
Discussor: Frank Bortone, M.D., F.C.C.P., Jersey City, New Jersey
"Interesting Cases of Chest Pathology."
Harrison S. Martland, M.D., Newark, New Jersey
Discussor: Irving L. Applebaum, M.D., F.C.C.P., Newark, N. J.
X-Ray Conference,
Merrill C. Sosman, M.D., Boston, Massachusetts, Moderator

PENNSYLVANIA CHAPTER

The Pennsylvania Chapter will hold its spring meeting in Pittsburgh on June 1. The scientific program to be presented at the meeting is now being prepared. It is planned to hold an x-ray conference as a part of the meeting. Chapter members who are interested in presenting interesting cases for the conference are requested to communicate with Dr. J. V. Foster, Secretary-Treasurer of the Chapter, 900 North Second Street, Harrisburg, Pennsylvania.

LUNCHEON MEETING, PERUVIAN CHAPTER



Photograph taken at the Luncheon Meeting of the Peruvian Chapter, December 16, 1949, in honor of Dr. Juan R. Herradora, Jersey City, New Jersey. From left to right: Dr. Humberto Valderrama; Dr. Juan Escudero Villar; Dr. Max Espinoza Galarza; Dr. Juan Machiavello; Dr. Ramon Vargas Machuca, President; Dr. Ovidio Garcia Rosell, Regent; Dr. Herradora; Dr. Juan Werner, Governor; Dr. Leopoldo Molinari; Dr. Victor Tejada; Dr. Angel Luis Morales; and Dr. Victor Narvaez.

PERUVIAN CHAPTER

The Peruvian Chapter held a luncheon meeting on December 16, 1949, at the Club de la Unión, Lima, in honor of the visit of Dr. Juan A. Herradora, Jersey City, New Jersey, Secretary of the Council on Pan American Affairs of the College. Dr. Ramón Vargas Machuca, President of the chapter, addressed the members present and welcomed Dr. Herradora. Dr. Herradora stated that he had a message from the President of the College to greet the members of the Peruvian Chapter and to invite them to the College meetings to be held in San Francisco, California, June 22-25, and in Rome, Italy, September 17-22, 1950.

The annual meeting of the Peruvian Chapter was held on December 28, 29 and 30, 1949, at the Dispensario Central Antituberculoso in Lima. The following scientific program was presented:

"Consideraciones Sobre la Terapéutica Actual en Tuberculosis,"
Ovidio García Rosell, M.D., F.C.C.P.

"Quimiografía del Diafragma,"
Max Espinoza Galarza, M.D., F.C.C.P.

"La Resistencia del Bacilo de Koch a la Estreptomicina,"
Leopoldo Molinari, M.D., F.C.C.P.

"Indice de Infección y Mortalidad en Magdalena Nueva,"
Manuel Agurto, M.D.

"El Problema de los Tuberculosos Incurables,"
Juan A. Werner, M.D., F.C.C.P.

"El Acido Para-amino Salicilico en los Empiemas,"
Juan Escudero Villar, M.D., F.C.C.P.

"Tuberculosis Fibrocaseosa Pulmonar Tratados con Métodos Combinados de Neumotórax y Estreptomicina,"
Victor Tejada, M.D., F.C.C.P. and Victor Narvaez, M.D.

"La Histopatología de la Caverna Tuberculosa,"
Humberto Valderrama, M.D.

"Resultados Alejados de la Neumectomía en la Tuberculosis Pulmonar,"
Alejandro Flores, M.D.

"Consideraciones Sobre el Temario del Segundo Congreso Argentino de Tisiología (Vacunación BCG, Antibióticos y Tuberculosis de las Serosas),"
Luis Cano Gironda, M.D., F.C.C.P.

"Consideraciones Sobre el Empleo de la Estreptomicina en el Medio Dispensarial,"
Ramón Vargas Machuca, M.D., F.C.C.P.

"El Tratamiento de la Tuberculosis con PAS y Estreptomicina,"
Leopoldo Molinari, M.D., F.C.C.P.

At a business meeting which followed the last scientific session, the following officers of the Peruvian Chapter were elected for the year:

Juan Escudero Villar, M.D., President
Leopoldo Molinari, M.D., Vice-President
Angel Luis Morales, M.D., Secretary
Luis E. Hubner, M.D., Treasurer
Alejandro Flores, M.D., Historian

PHILIPPINE CHAPTER

The Philippine Chapter held a meeting in October of 1949 to discuss the participation of the chapter in the First International Congress on Diseases of the Chest which is to be held in Rome in September of this year. Another meeting was held on October 29, 1949 to discuss future

plans and activities of the chapter and to take final action concerning participation in the Rome Congress. Drs. Miguel Canizares and Manuel Quisumbing, Sr. will be official delegates to the Congress.

On Thursday, March 16, 1950, the Philippine Chapter held its Inaugural Program and First Annual Meeting at the Session Hall, Quezon Institute, Quezon City. The following program was presented:

Welcome Address, Manuel Quisumbing, M.D., F.C.C.P., Governor of the College for the Philippines

Presidential Address, Miguel Canizares, M.D., F.C.C.P., Regent of the College for the Philippines

"BCG Vaccination in the Philippines," Sofia Bona de Santos, M.D., F.C.C.P.

"Occurrence of Bronchiectasis in Pulmonary Tuberculosis," Carmelo P. Jacinto, M.D., F.C.C.P., Heraldo del Castillo, M.D., F.C.C.P. and Adolfo Baviera, M.D., F.C.C.P.

Panel Discussions, Jose R. Celis, M.D., F.C.C.P., Moderator

"BCG Vaccination," Manuel V. Arguelles, M.D., Alberto V. Tupas, M.D. and Renato Ma. Guerrero, M.D.

"Bronchiectasis in Pulmonary Tuberculosis," Gonzalo F. Austria, M.D., Enrique Garcia, M.D. and Paterno Chikiamco, M.D.

A business meeting followed the scientific program at which time the following officers for 1950 were elected:

Miguel Canizares, M.D., President
Wenceslao Vitug, M.D., Vice-President
Fidel R. Nepomuceno, M.D., Secretary-Treasurer

Photograph taken at the Philippine Chapter meeting, held on October 29, 1949. Left to right, facing camera: Dr. J. Punzalan; Dr. F. Roque; Dr. Manuel Quisumbing, Sr., Governor; Dr. Miguel Canizares, Regent and President; Dr. F. R. Nepomuceno, Secretary-Treasurer; Dr. W. Vitug, Vice-President; Dr. H. del Castillo; Dr. L. Salas-Curtin; and Dr. C. Lorenzo.

POTOMAC CHAPTER

The Potomac Chapter of the College held its annual meeting in conjunction with the Maryland State Medical Society meeting in Baltimore on Wednesday, April 26. The following program was presented:

Panel Discussion: "The Pneumonias,"
Lawrence M. Serra, M.D., F.C.C.P.,
Baltimore, Maryland, presiding

"Acute Bacterial Pneumonias,"
Philip A. Tumulty, M.D., Baltimore, Maryland

"Viral Pneumonias Including Primary Atypical Pneumonia,"
Theodore E. Woodward, M.D., Baltimore, Maryland

"Suppurative Pneumonias (Lung Abscess),"
Brian Blades, M.D., F.C.C.P., Washington, D. C.

VIRGINIA CHAPTER

The Virginia Chapter of the College held its annual meeting on March 30 at the University of Virginia, Charlottesville. The following scientific program was presented:

"Tuberculosis of the Larynx,"
George Eward, M.D. and George Welchons, M.D., F.C.C.P., Richmond

"Pulmonary Lesions Simulating Tuberculosis,"
Woodbury Perkins, M.D., Charlottesville

"The Problem of Lung Cancer,"
E. C. Drash, M.D., F.C.C.P., Charlottesville

"Resection for Pulmonary Tuberculosis,"
F. P. Colemand, M.D., Richmond

"Vascular Anomalies of the Lung,"
Brian Blades, M.D., F.C.C.P., Washington, D. C.

WISCONSIN CHAPTER

The Wisconsin Chapter of the College met at the Medford Hotel, Milwaukee, on Friday, March 31. Dr. O. A. Sander presented the subject "Beryillosis." The presentation was followed by a round table discussion.

College News Notes

Dr. Russell H. Frost formerly of St. Paul, Minnesota, has been appointed Medical Director of Glen Lake Sanatorium, Oak Terrace, Minn.

Dr. Oscar Auerbach, Chief of the Laboratory Service, Halloran Veterans Administration Hospital, participated in a panel discussion on Tuberculosis in Children presented at the clinical session on chronic pulmonary diseases of the Tuberculosis Sanatorium Conference of Metropolitan New York on April 12 at the Cornell University Medical College Amphitheatre.

Dr. William A. Hudson, Detroit, Michigan, spoke before the Harris County Medical Society at their meeting in Houston, Texas on March 8. His subject was "Blood Spitting." On March 9, Dr. Hudson spoke before the Science Group at Texas Christian University on the subject "Some Thoughts Concerning the Origin and Advancement of Scientific Information," which was illustrated by lantern slides and motion pictures.

Dr. Paul H. Holinger, Chicago, Illinois, gave a presentation at the March 7 meeting of the Hudson County Medical Society in Jersey City, New Jersey. Dr. Holinger spoke on "The Clinical Significance of Bronchial Obstruction."

Professor Charles Gernez, director of the Pasteur Institute de Lille, France, visited the Bronchoscopic Clinic of the Ellis Hospital, Schenectady, New York, on April 5. Professor Gernez attended the International Congress of Silicosis, Sydney, Australia, as a delegate of the French Government. While in Schenectady, Professor Gernez was the guest of Dr. Arthur Q. Penta.

AMERICAN ACADEMY OF GENERAL PRACTICE

Dr. Walter Alvarez, senior consultant in the Division of Medicine, Mayo Clinic, has been appointed medical editor of "GP," published by the American Academy of General Practice. Dr. Alvarez succeeds Dr. F. Kenneth Albrecht, who died following an automobile accident last month. Dr. Albrecht was a Fellow of the American College of Chest Physicians.

The Academy is to be congratulated on the excellent new journal now being published which will undoubtedly be a valuable contribution to the medical literature.

The following Fellows of the American College of Chest Physicians serve on the Editorial Advisory Board on Diseases of the Chest of the "GP" journal: Dr. Andrew L. Banyai, Milwaukee, Wisconsin; Dr. Alvan L. Barach, New York City; Dr. Jay Arthur Myers, Minneapolis, Minnesota; and Dr. Maurice Segal, Boston, Massachusetts.

AMERICAN CANCER SOCIETY

The American Cancer Society has made available for 1950, 31 fellowships in Exfoliative Cytology at eleven laboratories throughout the country. For information concerning the regulations for these fellowships, and the laboratories where they are available, please write to the American Cancer Society, Inc., 47 Beaver Street, New York, N. Y.

Medical Service Bureau

POSITIONS AVAILABLE

Physicians wanted, salary $6,000 to $7,500 depending upon qualifications, training, etc. No maintenance, 5-day week. Private practice permitted. Large metropolitan midwest sanatorium. For further information please address Box 211A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Ill.

Tuberculosis staff physician wanted, 104-bed new state tuberculosis hospital in city of 45,000 in southwest Louisiana. Experience in tuberculosis not necessary. Must have Louisiana license or be eligible for reciprocity. Hospital has all medical and surgical facilities for treatment of tuberculosis. Maintenance for single man can be furnished but housing is available outside and nearby for family man. Opening at present for temporary or permanent applicant, salary $400 per month. Apply immediately to Dr. J. O. Duhon, Lafayette Charity Hospital, Lafayette, La.

Two full time staff physicians with at least one year's training and experience in tuberculosis wanted for 250 bed tuberculosis hospital in Ohio. Salary from $5,500 to $6,500 per year plus full maintenance for doctor and family. Active medical and surgical service, broad program of case finding and tuberculosis program being organized. Please address Box 212A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Positions open for physicians in large tuberculosis hospital. Salaries from $4,500 to $7,320 annually. Must be eligible for license to practice in Georgia. Contact Personnel Office, Battey State Hospital, Rome, Georgia.

There are several vacancies for Resident Physicians on Medicine at Triboro Hospital, effective July 1, 1950. Triboro Hospital is a municipal tuberculosis institution with 625 beds. The educational opportunities are excellent and there is a good training program. The residency is approved and for those who wish to qualify for their Boards in Internal Medicine, credit is given for one year's training at Triboro. The salary is $1,560 and single maintenance. Those interested please write or phone the Medical Superintendent, Triboro Hospital, Jamaica 2, L. I., N. Y.

Wanted immediately, resident physician. Good salary and maintenance. Call or write medical superintendent, Deborah Sanatorium, Browns Mills, New Jersey.

Staff physician for 105 bed private tuberculosis sanatorium in central Pennsylvania. Medical and surgical phases covered, including bronchoscopy, out-patient service. Excellent opportunity to learn. Pennsylvania license or reciprocity required. House and maintenance for physician and family, congenial surroundings. Inquire medical director or superintendent, Devitt's Camp, Allenwood, Pa.

SPECIAL PILLING INSTRUMENT USED IN NEW HEART OPERATION

An operation on the aortic valve, first of its kind in medical history, was recently performed successfully at Episcopal Hospital, Philadelphia.

A special instrument designed by the surgeons, and made by George P. Pilling and Son Co., 136 year old internationally known surgical instrument house, was used to force open a diseased valve, which would not open and close fully. The instrument, made of stainless steel, is still so new that it has no name although Filling workmen call it an aortic valve dilator.

The operation was performed by three surgeons of the thoracic surgery department of the hospital. Reportedly, it was the first time a heart operation had been performed without opening the chest. As to procedure, the carotid artery was cut and tied off and the instrument, a long steel tube, was inserted in the artery until the rounded point touched the valve. After gentle probing had located the valve opening, the dilator was inserted an additional one and one-half inches. A ratchet at the instrument handle was turned, which raised a flange near the tube end. This opened the diseased sections of the valve. The dilator was withdrawn four minutes later. It is thought that the procedure may be repeated if the valve becomes blocked again.

SANATORIUM DIRECTORY

The sanatoria listed in this section are among the finest private sanatoria in the United States. They are prepared to offer private, individual, specialized care to your patients.

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For listings in the SANATORIUM DIRECTORY write to the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois

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SPRINGFIELD, ILLINOIS

SOUTHERN SIERRAS SANATORIUM
BANNING, CALIFORNIA

SOUTHWESTERN PRESBYTERIAN SANATORIUM
ALBUQUERQUE, NEW MEXICO

THE SAMUEL AND NETTIE BOWNE HOSPITAL
POUGHKEEPSIE, NEW YORK

SANATORIO ALBERTAL
BUENOS AIRES, ARGENTINA

SANATORIO SAN ANGEL
MEXICO CITY, MEXICO

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Jay Arthur Myers, M.D., F.C.C.P., Chairman, Editorial Board.